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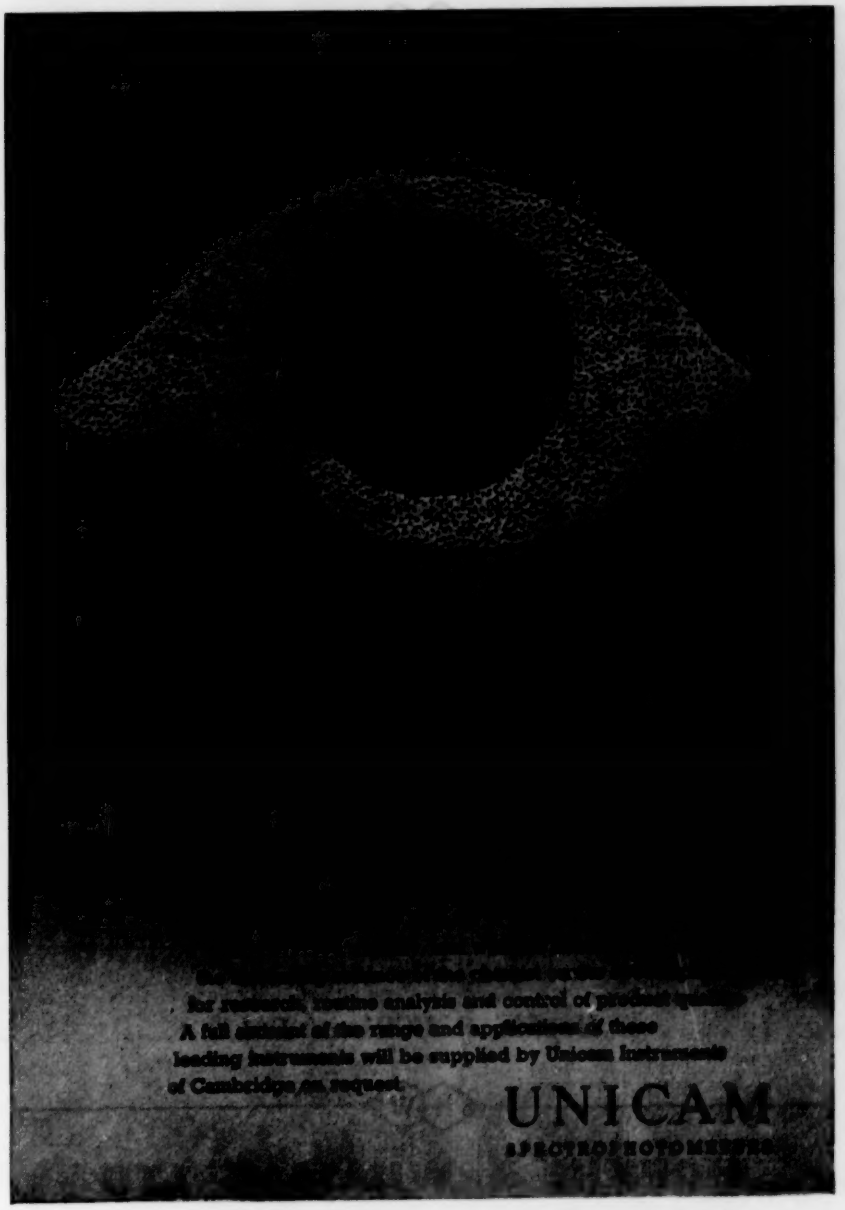
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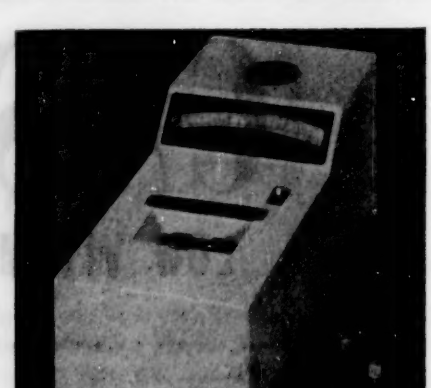

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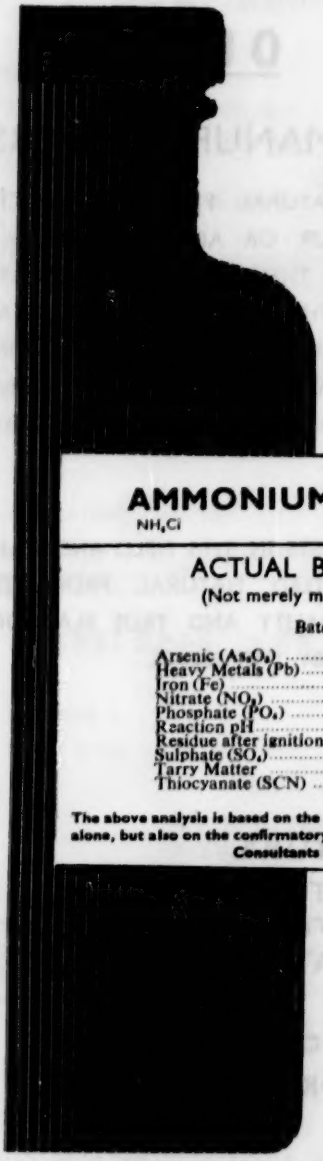

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(Not merely maximum impurity values)

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Heavy Metals (Pb)	0·0004%
Iron (Fe)	0·00001%
Nitrate (NO_3)	0·00005%
Phosphate (PO_4)	0·00002%
Reaction pH	5·1
Residue after ignition	Nil
Sulphate (SO_4)	0·0005%
Tarry Matter	Nil
Thiocyanate (SCN)	0·001%

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JOURNAL
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Thiadiazoles. Part I. The Oxidation of Amidinothiourea.

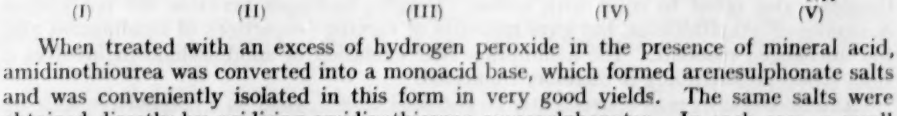
By FREDERICK KURZER.

[Reprint Order No. 5513.]

Oxidation, by hydrogen peroxide or iodine, cyclises amidinothiourea to 3 : 5-diamino-1 : 2 : 4-thiadiazole. Some properties of this base are described and reasons for the suggested structure given. Both amidinothiourea and its oxidation product are conveniently characterised as arenesulphonate salts.

ARYLTHIOUREAS can be oxidised to so-called " Hector bases " for which a thiadiazolidine structure (I) is generally accepted (Hector, *Ber.*, 1889, **22**, 1177; **1890**, **23**, 357; Fromm and Heyder, *Ber.*, 1909, **42**, **3804**; Lal and Krall, *J. Indian Chem. Soc.*, 1939, **16**, 31); aromatic thioamides similarly yield 3 : 5-diaryl-1 : 2 : 4-thiadiazoles (II) (Hofmann and Gabriel, *Ber.*, 1892, **25**, 1578; Walther, *J. pr. Chem.*, 1904, **69**, 44). The mechanism of these and other syntheses of 1 : 2 : 4-thiadiazoles is generally obscure (cf. Bambas, " The Chemistry of Heterocyclic Compounds," Interscience Publishers Inc., New York, 1952, Vol. IV, p. 35). The work reported in this series of papers aims at the unequivocal synthesis of 1 : 2 : 4-thiadiazoles.

The present paper describes the oxidation of amidinothiourea by hydrogen peroxide and iodine in ionising media. Both reagents yield the same product, which, on the basis of its formation and properties, is regarded as 3 : 5-diamino-1 : 2 : 4-thiadiazole (III). The reaction is thus comparable with the synthesis of 3 : 5-di-*p*-tolyl-1 : 2 : 4-thiadiazole (II; R = *p*-Me·C_6H_4) by the iodine oxidation of an *N*-arylimidoylarylthioamide, R·C(:NH)·NH·CS·R (Ishikawa, *Sci. Papers Inst. Phys. Chem. Res. Tokyo*, 1928, **7**, 237).



(I) (II) (III) (IV) (V)

When treated with an excess of hydrogen peroxide in the presence of mineral acid, amidinothiourea was converted into a monoacid base, which formed arenesulphonate salts and was conveniently isolated in this form in very good yields. The same salts were obtained directly by oxidising amidinothiourea arenesulphonates. In each case, a small proportion (5—6%) of the starting material was desulphurised hydrolytically to amidinourea. In contrast to amidinothiourea, which is instantly desulphurised in the cold by lead salts in alkaline solution, the oxidation product precipitated lead as the sulphide only on heating. This reaction proved a convenient means for testing for completeness of oxidation.

The oxidation of thiourea in ionising media yields the symmetrical " dithioformamidine," $[NH_2 \cdot C(:NH) \cdot S \cdot]_2$ (Claus, *Annalen*, 1875, **179**, 139; Werner, *J.*, 1912, **101**, 2177; Fromm and Heyder, *loc. cit.*). A possible analogous disulphide structure (IV) for the present products, almost indistinguishable analytically from (III), was eliminated by molecular-weight determinations, and by the relative stability of the free base. 3 : 5-Diamino-1 : 2 : 4-thiadiazole (III) was unaffected by prolonged treatment with 10% ammonia or pyridine at 100°; although the compound was decomposed by strong alkalis on heating.

it was sufficiently stable to be isolated from its salts by cold aqueous sodium hydroxide. Free dithioformamidine, on the other hand, is not known; the base decomposes instantly with elimination of sulphur when attempts are made to liberate it from its salts (McGowan, *J.*, 1886, **49**, 191; Remsen and Turner, *Amer. Chem. J.*, 1901, **25**, 190; Fromm and Heyder, *loc. cit.*).

Iodine reacted with amidinothiourea, to yield the same product as hydrogen peroxide. The method offered no advantage from the preparative point of view, but allowed the uptake of the oxidising agent to be observed quantitatively. Although theory required consumption of two equivalents of halogen, reaction in alcohol ceased after absorption of only one equivalent of iodine: 3 : 5-diamino-1 : 2 : 4-thiadiazole hydriodide was isolated in 32—35% yield; the mother-liquors contained much unchanged starting material as the hydriodide, which resists oxidation by iodine as was shown in a separate experiment.

$$2NH_2\cdot C(:NH)\cdot NH\cdot CS\cdot NH_2 + I_2 \longrightarrow NH_2\cdot C(:NH)\cdot NH\cdot CS\cdot NH_2,HI + C_3H_4N_4S,HI(\text{as III}) \quad (1)$$

In aqueous solution, the iodine oxidation of amidinothiourea was reversible, and, as with thiourea (cf. Marshall, *Proc. Roy. Soc. Edin.*, 1902, **24**, 233; Reynolds and Werner, *J.*, 1903, **83**, 1; Werner, *ibid.*, 1912, **101**, 2166, 2179), the completeness depended on the concentration of the reactants. In sufficiently great dilution (<0·066M; cf. Table, p. 5), the halogen consumption was in conformity with the production of the heterocyclic system (equation 1): spontaneous evaporation of suitable reaction mixtures afforded 3 : 5-diamino-1 : 2 : 4-thiadiazole in 65—70% yield.

$$NH_2\cdot C(:NH)\cdot NH\cdot CS\cdot NH_2 + I_2 \rightleftharpoons C_3H_4N_4S,HI\ (\text{as III}) + HI \quad . \quad . \quad . \quad . \quad (2)$$

Zinc and hydrochloric acid reconverted 3 : 5-diamino-1 : 2 : 4-thiadiazole almost quantitatively into amidinothiourea. In this respect, the compound differs from other 1 : 2 : 4-thiadiazoles (*e.g.*, I, II), which on reduction lose sulphur and yield substituted amidines or guanidines as main products (Hector, *Ber.*, 1892, **25**, 799; Ishikawa, *Sci. Papers Inst. Phys. Chem. Res. Tokyo*, 1925, **3**, 147).

The removal of two atoms of hydrogen from amidinothiourea may, theoretically, cause an alternative mode of ring closure, and affect two imino- instead of one thiol and one imino-groups. 3-Amino-5-mercapto-1 : 2 : 4-triazole (V) which would result by this cyclisation, however, has previously been synthesised by other routes (Fromm *et al.*, *Annalen*, 1922, **426**, 313; 1924, **437**, 108; Arndt and Milde, *Ber.*, 1921, **54**, 2089; 1922, **55**, 341), and differs from the base obtained in the present work. The behaviour, on attempted oxidation, of an amidinothiourea structure having its thiol group blocked by a substituent was in agreement with the above observation. *N*-Amidino-*S*-ethylthiourea did not decolorise iodine even in dilute aqueous solution. Diguanide, $NH_2\cdot C(:NH)\cdot NH\cdot C(:NH)\cdot NH_2$, containing imino-groups situated exactly as in amidinothiourea, also failed to react with iodine. Finally, hydrogen peroxide did not cyclise *N*-amidino-*S*-ethylthiourea, but gave mixtures of varying proportions of amidinourea and the unchanged reactant. The assumption that oxidation of amidinothiourea involves a thiol group preferentially is therefore confirmed.

Amidinothiourea may conveniently be obtained in 60% yield on a preparative scale by passing hydrogen sulphide through an aqueous solution of dicyandiamide at 70—80°. This is a modification of Bamberger's method (*Ber.*, 1883, **16**, 1461) and permits the free base to be isolated directly. A small amount of dithiobiuret is produced in the reaction, doubtless by interaction between amidinothiourea and excess of hydrogen sulphide.

Experimental

Light petroleum was of boiling range 60—80°.

Amidinothiourea (and 2 : 4-Dithiobiuret).—A solution of *N*-cyanoguanidine (42·0 g., 0·5 mole) in water (200 ml.) was kept at 75° during 12 hr., and at 65—70° during an additional 24—30 hr., while hydrogen sulphide was passed through it (2—3 bubbles per second). The resulting yellow liquid was cooled to 45°, made strongly alkaline with aqueous sodium hydroxide (40% w/v; 15 ml.), and filtered with suction. The filtrate, on slow cooling to room temperature, and storage at 0° for 24 hr., deposited prismatic leaflets. They were collected (filtrate A) and washed

with ice-water (3 × 20 ml.), and consisted of crude amidinothiourea [m. p. 162—164° (decomp.), after sintering at 154—158°; yield, 32·5—35·4 g., 55—60%]. Two crystallisations of the powdered solid from boiling methanol (8 ml. per g.; recovery per crystallisation, 65—70%) gave colourless massive lustrous prisms, m. p. 170—172° (decomp.) (Found: N, 47·2. Calc. for $C_2H_6N_4S$: N, 47·45%). The mother-liquors gave, on partial evaporation under reduced pressure, a crop of satisfactory quality.

Filtrate A was acidified to Congo-red with concentrated hydrochloric acid (25—30 ml.), a powdery precipitate separating and hydrogen sulphide being evolved simultaneously. After storage at 0° for 12 hr., the solid was collected (filtrate B) and washed with ice-water (3 × 30 ml.) (dry weight: 7·5—9 g.). It was stirred in water (120 ml.) at 95° for 2 min., and undissolved material (1—1·5 g., chiefly sulphur) removed by rapid filtration. The yellow filtrate deposited pale yellow needles, which were collected at 0° [m. p. 180—182° (decomp., after sintering at 172—175°); 5·5—7·0 g., 8—10%]. Further crystallisation, with addition of carbon, from water (12 ml. per g.; recovery 80—90%) gave needles of 2 : 4-dithiobiuret, m. p. 181—182° (decomp., after sintering slightly at 178—180°) (Found: C, 18·0; H, 3·8; N, 30·9; S, 46·9; 48·2. Calc. for $C_2H_5N_3S_2$: C, 17·8; H, 3·7; N, 31·1; S, 47·4%). Two additional crystallisations from ethanol–water (10 ml. each, per g.) raised the m. p. to 183—185° (decomp.).

Filtrate B was treated with toluene-*p*-sulphonic acid monohydrate (19·0 g., 0·1 mole) which dissolved rapidly. The separated crystalline amidinothiourea toluene-*p*-sulphonate was collected after 24 hr. at 0°, and washed with ice-water [m. p. 176—178° (decomp., after sintering at 170°); 16·5—18 g., 11—12·5%, calc. on the *N*-cyanoguanidine]. To this salt (14·5 g., 0·05 mole), mixed with water (10 ml.), aqueous sodium hydroxide (20 ml., 12% w/v, 0·06 mole) was added, and the stirred suspension warmed to 35°; dissolution occurred rapidly. Traces of undissolved impurities were quickly filtered off at the pump, and the filtrate was set aside at 0° for 24 hr.; prisms of amidinothiourea (3·8—4·4 g., 65—75%, calc. on the salt) separated.

Extending the time of reaction to 100 hr. increased the yield of dithiobiuret to 15—18%, but reduced that of amidinothiourea to 25%.

In previous syntheses of this compound (Rathke, *Ber.*, 1878, **11**, 963; Bamberger, *loc. cit.*; Slotta and Tschesche, *Ber.*, 1929, **62**, 1398; Thurston and Sperry, U.S.P. 2,364,594; Birtwell, Curd, Hendry, and Rose, *J.*, 1948, 1653), amidinothiourea was collected as a sparingly soluble salt from which the base was isolated by comparatively laborious methods.

The following were prepared from amidinothiourea (0·01 mole) and the appropriate sulphonic acid (0·012 mole) in water solution, and crystallised from aqueous ethanol (yields of uncrystallised salt in parentheses): *Toluene*-p-*sulphonate* (88%), m. p. 177—178° (decomp.) (Found: C, 37·1; H, 4·8; N, 19·9; S, 22·4. $C_9H_{14}O_3N_4S_2$ requires C, 37·2; H, 4·8; N, 19·3; S, 22·0%). m-*Nitrobenzenesulphonate* (95%), m. p. 205—206° (decomp.) (Found: C, 30·2; H, 3·7; N, 22·1. $C_8H_{11}O_5N_5S_2$ requires C, 29·9; H, 3·4; N, 21·8%). *Benzenesulphonate* (30%), m. p. 112—114° (decomp., after sintering at 100—104°) (Found: N, 19·9. $C_8H_{12}O_3N_4S_2$ requires N, 20·3%).

Amidinothiourea hydriodide was prepared (84%) by adding hydriodic acid (*d* 1·7; 13 g., 0·06 mole) to a suspension of powdered amidinothiourea (5·90 g., 0·05 mole) in boiling methanol (8 ml.). The *hydriodide* formed prisms, m. p. 186—187° (decomp.) [Found: I (Volhard), 52·3, 52·6. $C_2H_6N_4S,HI$ requires I, 51·6%].

Oxidation of Amidinothiourea by Hydrogen Peroxide.—(*a*) To a boiling solution of amidinothiourea (11·8 g., 0·1 mole) in ethanol (96%, 250 ml.), concentrated hydrochloric acid (10 ml., 0·1 mole) was added, followed by aqueous hydrogen peroxide (6% w/v; 170 ml., 0·3 mole) during 20—25 min. Most of the ethanol was removed under reduced pressure during 20—25 min. and the warm residual colourless liquid (180—200 ml.) treated with toluene-*p*-sulphonic acid monohydrate (23·75 g., 0·125 mole), which dissolved instantly. After 12 hr. at 0°, the product was collected and washed with the minimum of ice-water [m. p. 230—234° (decomp.), after sintering at 226—228°; 18·7—21·9 g., 65—76%] (aqueous filtrates A). Two crystallisations from 96% ethanol–light petroleum (20 and 8 ml., respectively, per g.; recovery per crystallisation, 80%) gave platelets of 3 : 5-*diamino*-1 : 2 : 4-*thiadiazole toluene*-p-*sulphonate*, m. p. 238—240° (decomp.) (Found: C, 37·3; H, 3·9; N, 19·4; S, 21·9. $C_9H_{12}O_3N_4S_2$ requires C, 37·5; H, 4·2; N, 19·4; S, 22·2%), very sparingly soluble in boiling absolute ethanol, soluble in boiling ethanol containing small percentages of water. A solution of the salt in cold 12% aqueous sodium hydroxide remained clear on dropwise addition of aqueous lead acetate; lead sulphide was only precipitated on heating.

The aqueous filtrate A was allowed to evaporate spontaneously at room temperature to small

volume (50—60 ml.). Two crystallisations of the collected solid (3·4—4 g.) from 95% ethanol gave platelets (1·35—1·65 g., 5—6%) of amidinourea toluene-*p*-sulphonate, m. p. and mixed m. p. (Haag, *Annalen*, **1862**, **122**, 25) 238—242° (decomp.) (Found: C, 39·9; H, 5·1. Calc. for $C_9H_{14}O_4N_4S$: C, 39·4; H, 5·1%). The material gave the characteristic yellow nickel salt on addition of nickel chloride (Grossmann and Schück, *Ber.*, 1906, **39**, 3357).

(*b*) The *m*-nitrobenzenesulphonate was similarly obtained as a pale buff solid, m. p. 228—230° (decomp.), after sintering at 222—226° (91%). Two crystallisations from 96% ethanol–light petroleum (70 and 40 ml. per g., respectively; recovery per crystallisation, 80%) gave the *m-nitrobenzenesulphonate* as a buff crystalline powder, m. p. 226—228° (decomp., after sintering at 224—226°) (Found: N, 21·3; S, 20·2. $C_8H_9O_8N_5S_2$ requires N, 21·9; S, 20·1%).

(*c*) Similarly, there was obtained (35%) 3 : 5-*diamino*-1 : 2 : 4-*thiadiazole benzenesulphonate*, forming platelets, m. p. 229—231° (decomp., after sintering at 226°), from ethanol (Found: C, 34·7; H, 3·5. $C_8H_{10}O_3N_4S_2$ requires C, 35·0; H, 3·65%).

(*d*) *Direct oxidation of amidinothiourea arenesulphonates by hydrogen peroxide.* A boiling solution of amidinothiourea *m*-nitrobenzenesulphonate (3·21 g., 0·01 mole) in aqueous ethanol (75%; 20 ml.) containing hydrochloric acid (1 ml., 0·01 mole) was treated with hydrogen peroxide (6%; 17 ml., 0·03 mole). The resulting liquid, when diluted with ethanol (10 ml.) and cooled to 0°, deposited a crystalline solid (2·40 g., 75%) which gave, on crystallisation (*cf.* example *b*), 3 : 5-diamino-1 : 2 : 4-thiadiazole *m*-nitrobenzenesulphonate, m. p. and mixed m. p. (specimen *b*) 226—228° (decomp. after sintering at 224°). Other amidinothiourea arenesulphonates were similarly oxidised.

Oxidation of Amidinothiourea by Methanolic Iodine.—Amidinothiourea (5·90 g., 0·05 mole), dissolved in hot methanol (150 ml.), was treated, at 30°, with a solution of iodine (6·35 g., 0·05 g.-atom) in methanol (40 ml.) during 1—2 min. All but the last 1—2 ml. of the iodine solution were instantly decolorised. The liquid was rapidly evaporated in a vacuum (bath-temp., 40—45°; 15—20 min.; severe frothing) to small volume (70—80 ml.). The residual orange-brown liquid was gently agitated and slowly diluted with ether (300—350 ml.); crystallisation was completed by storage at 0° during 24 hr. The collected material (filtrate A) was washed with ether, and formed a white crystalline powder (3·90—4·25 g., 32—35%) of 3 : 5-*diamino*-1 : 2 : 4-*thiadiazole hydriodide*, m. p. 174—178° (decomp.) [Found: I (Volhard), 52·3, 51·6. $C_2H_4N_4S,HI$ requires I, 52·0%].

The methanol-ethereal filtrates A, on gradual dilution with light petroleum (3 × 100 ml., at 1-hr. intervals), and storage at 0°, deposited more crystalline material (3·0—3·3 g.), consisting of impure amidinothiourea hydriodide. This was identified by conversion into the toluene-*p*-sulphonate, m. p. and mixed m. p. 175—178° (decomp.) [2·9 g., corresponding to 20% unchanged starting material].

Conversion of hydriodide into arenesulphonates. The above hydriodide (2·45 g., 0·01 mole), dissolved in cold water (20 ml.), was treated with a saturated aqueous solution of the appropriate sulphonic acid (0·012 mole); the following salts (yields of uncrystallised product in parentheses) were prepared: Toluene-*p*-sulphonate (80%), m. p. and mixed m. p. 236—240° (decomp.) (Found: C, 37·6; H, 4·2; N, 19·6%). *m*-Nitrobenzenesulphonate (82%), m. p. and mixed m. p. 226—229° (decomp., after sintering at 223—226°) (Found: C, 30·0; H, 2·9. Calc. for $C_8H_9O_8N_5S_2$: C, 30·1; H, 2·8%). Benzenesulphonate (54%), m. p. and mixed m. p. 228—231° (decomp., after sintering at 225°) (Found: N, 20·8; S, 23·6. Calc. for $C_8H_{10}O_3N_4S_2$: N, 20·4; S, 23·4%).

Treatment of Amidinothiourea Hydriodide with Methanolic Iodine.—A solution of the reactant (0·01 mole) in warm methanol (8 ml.) was treated with iodine (0·01 mole) in methanol (15 ml.); no decolorisation occurred and amidinothiourea was recovered as the toluene-*p*-sulphonate, m. p. and mixed m. p. 175—177° (decomp.) (total yield, 1·95 g., 68%). In dilute aqueous solution (2·5% w/v), however, amidinothiourea hydriodide decolorised an equimolecular quantity of iodine.

Oxidation of Amidinothiourea by Aqueous Iodine.—A solution of amidinothiourea (1·18 g., 0·01 mole) in water (80 ml.) was treated, at room temperature, with N-iodine (20 ml.). Almost all the iodine was decolorised; the pale yellow liquid was treated with toluene-*p*-sulphonic acid monohydrate (2·85 g., 0·015 mole), and set aside for spontaneous evaporation nearly to dryness. The crystalline pink to violet solid was collected, washed with water (3 × 4 ml.), and fractionated by crystallisation from 96% ethanol. The less soluble product was the toluene-*p*-sulphonate of 3 : 5-diamino-1 : 2 : 4-thiadiazole, m. p. and mixed m. p. 236—238° (decomp.) (total, 1·85 g., 65%), the more soluble material that of amidinothiourea, m. p. and mixed m. p. 176—178° (decomp.) (0·35 g., 12%).

Effect of the Concentration of Amidinothiourea on the Completeness of Oxidation (by Aqueous Iodine).—(i) Portions of amidinothiourea (0·59 g., 0·005 mole), dissolved in the appropriate volume of water (Table, line 2), were titrated with N-iodine, completeness of reaction being tested for by starch solution. The "end-point" was taken when the blue colour produced by starch and successive drops withdrawn ½, 1, and 1½ min. after the addition of iodine was of reasonably undiminished intensity. However, this point could not be determined with accuracy, particularly in the more concentrated solutions.

(ii) Portions of amidinothiourea (0·59 g., 0·005 mole), dissolved in the appropriate volume of water (Table, line 2), were treated with aqueous N-iodine (10 ml., 0·005 mole) at room temperature. After 2 min., the unused iodine was titrated with 0·1N-sodium thiosulphate, starch being used as external indicator. In experiments 5—7, the "end-point" was ill-defined. The results of experiments (i) and (ii) are summarised in the Table.

Experiment (i)

Run	1	2	3	4	5	6	7	8
Water (ml.)	140	90	65	40	30	20	10	5
N-Iodine absorbed (ml.)	9·8	9·6	9·3	8·9	8·2	7·8	6·8	6·0
Molarity of amidinothiourea at "end-point"	0·033	0·050	0·066	0·102	0·13	0·18	0·29	0·45
Mols. of iodine absorbed *	0·98	0·96	0·93	0·89	0·82	0·78	0·68	0·60

Experiment (ii)

Molarity of amidinothiourea	0·033	0·050	0·066	0·100	0·125	0·166	0·250
Mols. of iodine absorbed *	0·99	0·99	0·95	0·88	0·84	0·75	0·65

* Per mol. of amidinothiourea.

3 : 5-*Diamino*-1 : 2 : 4-*thiadiazole*.—A cooled suspension of the toluene-*p*-sulphonate (5·75 g., 0·02 mole) or the hydriodide (4·9 g., 0·02 mole) of this base in water (8 ml.) was slowly treated with aqueous sodium hydroxide (50% w/v; 2·4 ml., 0·03 mole). The warm (30—35°) solution was quickly filtered to remove traces of insoluble impurities and set aside at 0° for 48 hr. The separated prisms (m. p. 163—167°; 1·48—1·75 g., 64—76%) were collected, and gave, after two crystallisations from ethanol–light petroleum (10 and 3 ml., respectively, per g.; recovery per crystallisation, 80—90%), prisms of **3 : 5-*diamino*-1 : 2 : 4-*thiadiazole***, m. p. 169—171° [Found: C, 21·2, 20·6; H, 3·3, 3·4; N, 49·2; S, 28·0; *M* (cryoscopic) in thymol, 110, 115; in camphor, 130, 140. $C_2H_4N_4S$ requires C, 20·7; H, 3·45; N, 48·3; S, 27·6%; *M*, 116], highly soluble in warm ethanol, acetone, and water, sparingly soluble in light petroleum.

A solution of the base in cold 12% alkali, when treated with aqueous lead acetate, only precipitated lead sulphide on subsequent heating. The compound was unaffected when its 5% solution in aqueous ammonia (10%), or in pyridine, was kept at 100° during 30 min. The identity of the base was confirmed by its reconversion into the toluene-*p*-sulphonate, m. p. and mixed m. p. 236—238° (decomp.), and the *m*-nitrobenzenesulphonate, m. p. and mixed m. p. 227—228° (decomp., after sintering at 225°).

Reduction of **3 : 5-*Diamino*-1 : 2 : 4-*thiadiazole***.—A suspension of **3 : 5**-diamino-1 : 2 : 4-thiadiazole toluene-*p*-sulphonate (2·30 g. 0·008 mole) in boiling absolute ethanol (30 ml.) was treated with zinc foil (4 g.), followed by concentrated hydrochloric acid (3 ml.), and the suspension was gently refluxed during 15 min. The liquid was decanted from the zinc (which was once again extracted with a little boiling ethanol), and the combined solution rapidly evaporated in a vacuum to small volume (6—8 ml.). Dilution of the clear colourless residual liquid with water (12 ml.) and addition of toluene-*p*-sulphonic acid monohydrate (0·95 g., 0·005 mole) gave, on storage at 0°, lustrous prisms [m. p. (174°) 176—178° (decomp.); 2·12 g., 91%] which, on crystallisation from ethanol, gave amidinothiourea toluene-*p*-sulphonate, m. p. and mixed m. p. 177—178° (decomp.).

N-Amidino-S-ethylthiourea Salts.—Amidinothiourea (11·8 g., 0·1 mole) in methanol (80 ml.) was refluxed with ethyl bromide (55 g., 0·5 mole) during 4 hr. After removal of the excess of the ethyl bromide and most of the solvent under reduced pressure, the residual colourless liquid (30 ml.) was diluted with acetone (25 ml.) and cooled; crystals appeared slowly. Separation of the product was completed by very gradual dilution of the crystallising mixture with ether (150—180 ml.; avoiding precipitation of the hydrobromide as an oil), followed by storage at 0°. The collected material was washed with ether, and formed prisms of *N*-amidino-*S*-ethylthiourea hydrobromide, m. p. 125—128° (decomp., after sintering at 115—120°) (17·0—19·3 g., 75—85%) (Found: C, 21·6; H, 4·6%). Two crystallisations from ethanol–ether raised the m. p. to 128—134° (decomp.) (Found: C, 21·8; H, 4·9; Br, 34·6. Calc. for $C_4H_{10}N_4S,HBr$: C, 21·2; H, 4·85; Br, 35·2%). [Slotta and Tschesche (*Ber.*, 1929, **62**, 1398) obtained this salt from

amidinothiourea carbonate, and give m. p. 166° (decomp.).] Amidinothiourea, being insoluble in boiling ethyl bromide, was recovered unchanged after prolonged refluxing with a large excess of this reagent.

Treatment of a solution of *N*-amidino-*S*-ethylthiourea hydrobromide (0·01 mole) in cold water (8 ml.) with toluene-*p*-sulphonic acid monohydrate (0·02 mole) afforded, after two crystallisations from ethanol (4 ml. per g.), prisms (91%) of N-*amidino*-S-*ethylthiourea toluene*-p-*sulphonate*, m. p. 151—153° (decomp.) (Found : C, 41·3; H, 5·6; N, 17·3; S, 19·7. $C_{11}H_{16}O_3N_4S_2$ requires C, 41·5; H, 5·7; N, 17·6; S, 20·1%). The m-*nitrobenzenesulphonate*, similarly prepared (92%), consisted of pale yellow prisms, m. p. 161—163° (decomp.) (from ethanol) (Found : C, 34·1; H, 4·3. $C_{10}H_{15}O_5N_5S_2$ requires C, 34·4; H, 4·3%).

Action of Iodine and Hydrogen Peroxide on N-*Amidino*-S-*ethylthiourea*.—(i) Aqueous or ethanolic N-iodine was not decolorised when added to 0·5M-aqueous or -ethanolic *N*-amidino-*S*-ethylthiourea hydrobromide at room temperature. (ii) A boiling solution of *N*-amidino-*S*-ethylthiourea hydrobromide (2·27 g., 0·01 mole) in absolute ethanol (15 ml.) was treated with hydrogen peroxide (6% w/v; 17 ml., 0·03 mole) during 15 min. The solution was distilled (to 20 ml.), and treated with toluene-*p*-sulphonic acid (3·44 g., 0·02 mole). The clear liquid was allowed to evaporate spontaneously at room temperature (to approx. 12 ml.). The crystals were collected (2·5 g.), powdered, and heated with absolute ethanol (6 and 2 ml.), and the mixture was filtered hot (filtrate A). The residual solid (1·45 g.) gave, after two or three crystallisations from 95% ethanol, prisms (1·15 g., 42%) of amidinourea toluene-*p*-sulphonate, m. p. and mixed m. p. 238—240° (Found : C, 39·1; H, 4·9; N, 19·9. Calc. for $C_9H_{14}O_4N_4S$: C, 39·4; H, 5·1; N, 20·4%). The hot ethanolic filtrate A was diluted with light petroleum (6 ml.) and deposited a product which consisted, after crystallisation from ethanol–light petroleum, of *N*-amidino-*S*-ethylthiourea toluene-*p*-sulphonate (0·55 g., 17%), m. p. and mixed m. p. 150—153° (decomp.). (iii) Aqueous solutions of diguanide sulphate (Ostrogovich, *Chem. Zentr.*, 1910, II, 1890; Rackmann, *Annalen*, 1910, **376**, 170) did not decolorise aqueous iodine.

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Homolytic Aromatic Substitution. Part VIII. Partial Rate Factors for the Phenylation of Toluene.*

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Partial rate factors are determined for the phenylation of toluene by an analysis of the products formed in the competitive phenylation of mixtures of toluene and nitrobenzene, and of toluene and pyridine. The proportions of the isomers formed in the phenylation of toluene are determined by infrared spectroscopy. It is shown that at higher concentrations of benzoyl peroxide toluene undergoes some substitution at the side chain with the formation of diphenylmethane. The partial rate factors for toluene show an overall activation of the molecule when compared with benzene. The sequence of activation shows the order $o > p > m$, the activity at the *meta*-position being little different from that of any position in benzene.

The determination of the partial rate factors for the phenylation of a monosubstituted benzene, PhR, has been reported for R = NO_2, F, Cl, Br, I, Ph, and Bu^t (Parts I—V and VII ; *J.*, 1951, 2892 ; 1952, 2094 ; 1953, 44, 3412 ; 1954, 794, 3352). In Part VII attention was drawn to the special difficulties which are encountered in attempts to determine the partial rate factors for the phenylation of alkylbenzenes because of the possibility of substitution in or hydrogen abstraction from the side chain by the free phenyl radical. These difficulties are absent in *tert.*-butylbenzene, but in the phenylation of toluene by means of benzoyl peroxide such side-reactions could lead to the formation of diphenylmethane by substitution, and of dibenzyl by hydrogen abstraction and subsequent

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dimerisation. In the early qualitative work on the reaction between benzoyl peroxide and toluene, however, there is no mention of the occurrence of either of these hydrocarbons (Gelissen and Hermans, *Ber.*, 1925, **58**, 476), but recently Dannley and Zaremsky have reported (124th Meeting of the American Chemical Society, September, 1953) the presence of diphenylmethane in the product from the reaction between benzoyl peroxide and toluene. In a subsequent paper (Dannley, Gregg, Phelps, and Coleman, *J. Amer. Chem. Soc.*, 1954, **76**, 445) on the phenylation of the halogenobenzenes it was observed that these workers used concentrations of benzoyl peroxide considerably higher than those used in our own work. A repetition of our method, using concentrations similar to those reported by Dannley and his co-workers, showed with the aid of infra-red spectroscopy that some diphenylmethane was in fact formed. When, however, the reaction was conducted under the conditions of concentration normally used by us in the determination of partial rate factors, it was confirmed that diphenylmethane was absent from the product, both by the use of infra-red analysis and by the application of other physical and chemical methods. It appears, therefore, that the facility of side-chain attack is dependent upon the concentration of the attacking free radicals and that by the use of radicals in high dilution it should be possible to determine the partial rate factors for the phenylation of toluene without the intrusion of complications arising from side-chain attack. On the other hand, with hydrocarbons containing more than one alkyl group, other than *tert.*-butyl, it is apparent that hydrogen abstraction from the side-chain takes place more readily because 4 : 4′-dimethyldibenzyl and 3 : 5 : 3′ : 5′-tetramethyldibenzyl have been isolated from the products of the reaction of benzoyl peroxide with *p*-xylene and mesitylene respectively (Augood, Hey, Nechvatal, Robinson, and Williams, *Research*, 1951, **4**, 386).

The apparent dependence of diphenylmethane formation on the concentration of benzoyl peroxide has some far-reaching consequences. If the nuclear and side-chain phenylation processes are simultaneous reactions of the same order, then the composition of the mixed product should be independent of the concentration of the reagents. The formation of diphenylmethane must therefore be a reaction of a higher order than the nuclear phenylation reaction, with respect to phenyl radicals, since its rate of formation increases the more rapidly with an increase in the concentration of free phenyl radicals. The mechanistic consequences of this observation will be elaborated in a later publication.

The influence of the methyl group on the nuclear phenylation of toluene at 80° has now been determined by means of competitive experiments with nitrobenzene, a large excess of an equimolar mixture of the competing solvents being used compared with the benzoyl peroxide used as the source of the phenyl radicals. Under these conditions more than 80% of the benzoyl peroxide was accounted for and the rate ratio $^{PhMe}_{PhNO_2}K$ was derived from an analysis of the mixture of substituted diphenyls by means of titrations with titanous chloride as used in Part II (*loc. cit.*). Nitrobenzene was used as the competing solvent because its comparatively high reactivity minimises the formation of resins. In cases where the two competing solvents are of low reactivity (*e.g.*, toluene and pyridine) the diaryls formed are considerably more reactive than the original solvents and the percentage of resins formed in such reactions therefore increases. The ratios of the isomeric methyldiphenyls formed in the phenylation of toluene have also been measured by means of infra-red spectroscopy, the spectra for each of the three pure isomerides having been first established.

Competitive experiments have also been carried out with the phenylation of mixtures of toluene and pyridine. In this instance this method is not entirely satisfactory on account of the formation of compounds of higher molecular weight, but the results obtained give general support to those derived from the competitive experiments between toluene and nitrobenzene, as indicated below.

Experimental Methods and Results

Reagents.—Nitrobenzene was purified as described in Part II (*loc. cit.*). Toluene (B.D.H.) was washed with concentrated sulphuric acid until the washings were colourless, then with water, and finally dried ($MgSO_4$). It was then refluxed over sodium and distilled twice through

a 6-ft. helix-packed column. Benzoyl peroxide was purified to constant m. p. 104·8° as described in Part II. Diphenylmethane was purified to constant m. p. 26° by fractional freezing. 4-Methyldiphenyl, m. p. 48°, was prepared by the method of Gomberg and Pernert (*J. Amer. Chem. Soc.*, 1926, **48**, 1372) and similar methods, starting from *m*-toluidine and *o*-toluidine respectively, were used for the preparation of 3- (b. p. 141°/14 mm.) and 2-methyldiphenyl (b. p. 138°/23 mm.) respectively. The yellow colour was removed from the last two hydrocarbons by shaking them with four portions of concentrated sulphuric acid and then with water before they were dried and distilled.

Direct Determination of $^{PhMe}_{PhNO_2}K$.—Benzoyl peroxide (6 g.) was allowed to decompose in an equimolar mixture (200 ml.) of toluene and nitrobenzene in a thermostat at 80° for 72 hr. The toluene was distilled off at atmospheric pressure through a 25-cm. helix-packed column, the jacket of which was electrically heated to the b. p. of the distilling solvent. As much nitrobenzene as possible was distilled off under reduced pressure (b. p. 136°/95 mm.) and the nitrobenzene distillate was redistilled at the same pressure, the final 5 ml. being added to the main product. This was done in order to ensure that no methyldiphenyls were lost in the nitrobenzene distillate. Since benzoic acid was found to be appreciably volatile in nitrobenzene but not in toluene, the nitrobenzene distillate was extracted with 2N-aqueous sodium hydroxide (100 ml.), which was subsequently employed to hydrolyse the main product. After hydrolysis for 12 hr. at 100°, the main product was extracted while hot with benzene (4 × 30 ml.), and the combined benzene extracts were well washed with sodium hydroxide solution (100 ml.) followed by water (50 ml.) and finally dried ($CaCl_2$; 24 hr.). The combined aqueous extracts, containing sodium benzoate and substituted sodium phenoxides, were acidified while hot with concentrated hydrochloric acid, neutralised with solid sodium hydrogen carbonate, and filtered. The filtrate, after extraction with ether (2 × 30 ml.) to remove phenols, was reacidified with concentrated hydrochloric acid and extracted quantitatively with methylene chloride (4 × 30 ml.). The aqueous layer was then discarded and the methylene chloride solution, after being dried ($CaCl_2$), was evaporated at room temperature, the residual benzoic acid being dried over concentrated sulphuric acid and then weighed (m. p. 119—120°). The benzene solution, containing the main product, was passed through a 15-cm. alumina column to remove tar, and the column was eluted first with benzene (100 ml.) and finally with a mixture of benzene (20 ml.) and ether (10 ml.). Under these conditions only tar is retained on the column, and the diaryls pass through without loss. Solvents were removed by distillation through the 25-cm. column mentioned above, and the residue was quantitatively transferred, by using benzene as wash-liquid, to a small fractionation apparatus which was equipped with a 10-cm. helix-packed column with electrically heated jacket (see Part II, *loc. cit.*). After removal of the wash-benzene at atmospheric pressure the bulk of the residual nitrobenzene was carefully distilled off (b. p. 142°/115 mm.). The nitrobenzene distillate was redistilled under the same conditions, the final fraction (3 ml.) remaining in the flask being retained (the pre-forerun). The main product (5 ml.) remaining in the flask was transferred to the small distillation apparatus (capacity 10 ml.) described in Part II, and the benzene used in the transference was carefully removed at atmospheric pressure. The pressure was then lowered to 0·1 mm. and two fractions were collected. The first fraction, termed the fore-run (b. p. 30—80°/0·1 mm.), consisted of nitrobenzene with some of the methyldiphenyls. It may be safely assumed that the fore-runs contained no nitrodiphenyls, since these were found not to distil until a temperature 43° above that at which the fore-runs were collected had been reached. The second fraction (b. p. 80—130°/0·1 mm.) was composed of methyl- and nitro-diphenyls. The residue in the flask amounted to less than 10% of the diaryl fraction and consisted mainly of tar not removed on the alumina column. Weighed portions of the pre-forerun, fore-run, and run were made up to the required strength with acetone and subsequently analysed for nitro-group by the titanous chloride method. The standard procedure described in Part II was employed. The pre-forerun was found to consist of pure nitrobenzene, thus showing that no methyldiphenyls had been lost in the distillation. The fore-runs were also analysed for nitrogen by the micro-Dumas method. After extraction of the runs with concentrated hydrochloric acid, they were analysed for nitrogen by the micro-Dumas method and the basic material from runs (1) and (2) amounted to 27 mg. and 31 mg. respectively. The results of these competitive reactions are summarised in Table 1. The comparatively small loss of benzoyl peroxide not accounted for is due in part to the polyaryl resin in which phenyl radicals are incorporated and in part to the fact that no attempt was made to isolate the benzene which is known also to be formed in a side-reaction.

Determination of Ratio of Isomerides formed in the Phenylation of Toluene.—Benzoyl peroxide was allowed to decompose in toluene at 80° in a thermostat. In experiments (3) and (4) 6 g.

of benzoyl peroxide and 200 ml. of toluene were used, in experiment (5) 15 g. and 500 ml., and in experiment (6) 26·7 g. and 93·5 ml. respectively. The mixtures of methyldiphenyls were isolated by the standard procedure described in Part II [Product from (3): Found, C, 92·6; H, 7·2. Product from (4): Found, C, 92·9; H, 7·3. Product from (6): Found, C, 92·5; H, 7·3. Calc. for $C_{13}H_{12}$: C, 92·8; H, 7·2%]. Each of the four products was chromatographed on alumina before distillation and in every case a resin was collected, having b. p. 130—170°/0·1 mm., which was presumed to consist substantially of higher phenylation products (Found: C, 91·4; H, 8·4%; *M*, 238). In reaction (6) a white solid (0·1 g.) separated from the original reaction mixture, which was identified as diphenyl-4-carboxylic acid, m. p. 215° and mixed m. p.

TABLE 1.

Experiment:	1	2	Experiment:	1	2
Diaryl fraction (g.)	1·7918	2·1344	N in run by micro-Dumas (%)	5·75	6·1
$Ph{\cdot}C_6H_4{\cdot}NO_2$ (%)	89·8	84·5	$Me{\cdot}C_6H_4{\cdot}Ph$ in fore-run (%)	12·7	10·7
Total $Ph{\cdot}C_6H_4{\cdot}NO_2$ (g.)	1·6091	1·8044	$Me{\cdot}C_6H_4{\cdot}Ph$ in fore-run (g.)	0·4942	0·3833
Fore-run (g.)	3·8760	3·5976	Total $Me{\cdot}C_6H_4{\cdot}Ph$ (g.)	0·6769	0·7133
N in fore-run by $TiCl_3$ (%)	10·0	10·2	$\frac{PhMe}{PhNO_2}K$	0·498	0·468
N in fore-run by micro-Dumas (%)	10·2	10·4	$Ph{\cdot}CO_2H$ (g.)	3·3	3·4
N in run by $TiCl_3$ (%)	5·95	6·3	$(Ph{\cdot}CO_2)_2$ accounted for (%)	81·5	84·5

Hence $\frac{PhMe}{PhNO_2}K = 0·48$.

TABLE 2.

Experiment	Diaryl fraction (g.)	Resin (g.)	Free $Ph{\cdot}CO_2H$ (g.)	$Ph{\cdot}CO_2H$ after hydrolysis (g.)	Peroxide accounted for (%)
3	2·144	1·945	Not extracted	1·4	80
4	2·069	2·188	,,	1·4	84
5	6·1	5·17	3·3	0·55	72
6	6·5	5·7	7·0	1·6	60

219—220°; this probably arises from phenylation of benzoic acid. The results of these reactions are summarised in Table 2.

The spectrographic analysis of the products of these reactions was carried out on a Grubb-Parsons single-beam instrument fitted with an automatic pen recorder. Nitromethane was used as solvent, since it had no pronounced bands in the range 11—15 mμ where the characteristic methyldiphenyl bands exist. The spectrum was recorded through a 130-mμ rock-salt cell with a speed of wave-length scanning and slit opening such that the energy of transmission recorded for the pure solvent was nearly constant over the required range. Owing to the low percentage of the *meta*- and *para*-isomerides found in the mixtures, very concentrated solutions had to be used in order to attain a sufficiently high degree of accuracy. For this purpose grade "A" 1-ml. volumetric flasks were used containing from 0·35 to 0·5 g. of mixture per ml. The calibration spectra of the pure 3- and 4-methyldiphenyl were taken with 0·05 g. in 1 ml. and that of the 2-methyldiphenyl with about 0·25 g. in 1 ml. The accuracy of the method was tested on two artificial mixtures (A) and (B) of known composition and the results are given in Table 3. The analyses of the products from reactions 3, 4, and 5 are reported in Table 4. Dannley and Zaremsky (*loc. cit.*) have reported *ortho*- 65%, *meta*- 19%, and *para*-substitution 16% for the phenylation of toluene.

TABLE 3. *Analysis of mixtures of methyldiphenyls.*

	Known composition (%)			Composition found (%)		
Solution	2-	3-	4-	2-	3-	4-
A	50	24	26	46	26	28
B	41	34	25	37	36	27

TABLE 4. *Analysis of product obtained in phenylation of toluene.*

	Composition (%)		
Solution	2-	3-	4-
3	70·6	17·0	12·4
4	70·1	17·0	12·9
5	71·8	16·1	12·0
Mean	70·8	16·7	12·4

In addition to the spectra of the three pure methyldiphenyls an examination of the spectrum of diphenylmethane showed a very intense band which was not quite coincident with a band common

to the three methyldiphenyls, whereas elsewhere in the relevant region diphenylmethane absorbed only very weakly. At the high concentrations of the mixtures used in the determination of the isomer ratios the peak characteristic of diphenylmethane would be swamped, but examination of more dilute solutions (0·1 g. in 1 ml.) of the products from reactions 3, 4, and 5 showed no trace of the presence of diphenylmethane. Addition of diphenylmethane to the mixtures could be detected in the spectrum down to a concentration of 4%. In mixture 6 at a concentration of 0·1 g. in 1 ml., the diphenylmethane band was very pronounced and a comparison with similar mixtures made up with known quantities of added diphenylmethane showed that mixture 6 contained approximately 15% of diphenylmethane.

Direct Determination of ${}^{PhMe}_{PyH}K$.—Experiments (7) and (8) were performed with an equimolar mixture of benzene and pyridine, using conditions already described. After hydrolysis the mixture was separated by extraction with aqueous hydrochloric acid (7N) and separated into neutral and basic portions. These were worked up separately and the weights of methyldiphenyls and of phenylpyridines were obtained. A high-boiling residue was obtained from the neutral portion and from its nitrogen content (1·4%) it is regarded as a 4 : 1 mixture of methylterphenyls and diphenylpyridines. A correction was made for this in the calculation of ${}^{PhMe}_{PyH}K$. The occurrence of diphenylpyridines in the residue obtained from the neutral portion of the product, thus demonstrating the feeble basicity of such compounds, had been observed in previous work (Part II). The results are recorded in Table 5.

TABLE 5.

Experiment :	7	8
Phenylpyridines (g.)	0·922	0·884
Methyldiphenyls (g.)	1·350	1·201
Benzoic acid (g.)	2·9	3·1
Residue (g.)	1·170	1·278
${}^{PhMe}_{PyH}K$	1·68	1·69
$(Ph\cdot CO\cdot O)_2$ accounted for (%)	87	88·5

This result gives a value of 1·75 for ${}^{PhMe}_{PhH}K$ (*i.e.*, ${}^{PhMe}_{PyH}K \times {}^{PyH}_{PhH}K = 1{\cdot}685 \times 1{\cdot}04$), but as a result of the relatively large amount of residue formed in these reactions this method for the determination of the rate ratio cannot, in this case, be considered to be very satisfactory. The results, however, do support, within the limits of the method, the rate ratio for toluene obtained by using nitrobenzene as the second solvent.

It is of interest that Professor R. Huisgen (personal communication) found a value of 1·9 for ${}^{PhMe}_{PyH}K$, using nitrosoacetanilide as a source of phenyl radicals, while Dr. R. L. Dannley (personal communication), using benzoyl peroxide, found a value of 1·4.

DISCUSSION

The rate of phenylation of toluene with reference to that of benzene as unit is given by ${}^{PhMe}_{PhNO_2}K \times {}^{PhNO_2}_{PhH}K$, *i.e.*, $0{\cdot}48 \times 4{\cdot}0$ (cf. Part II) $= 1{\cdot}9$. Use of this value and the mean values obtained by spectrographic analyses for the ratio of isomerides formed in the phenylation of toluene gives the following partial rate factors for this reaction :

$$F_o = 4{\cdot}1\,;\ F_m = 1{\cdot}0\,;\ F_p = 1{\cdot}4.$$

The high degree of activation of the *ortho*-position is noteworthy, whereas the introduction of the methyl group into benzene has no significant effect on the phenylation at the *meta*-position. Unlike *tert.*-butylbenzene (cf. Part VII, *loc. cit.*) the overall effect in toluene is one of mild activation with the notable absence of any steric influence. Wheland (*J. Amer. Chem. Soc.*, 1942, **64**, 900) calculated the atom localisation energies for free-radical substitution in toluene, and predicted that the observed sequence of activation should be o-, p- $> m$. This is now shown to be in agreement with experiment.

Thanks are accorded to Dr. D. R. Augood for help with preliminary experiments, and to the Department of Scientific and Industrial Research for the grant of a Maintenance Award to B. W. P.

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The Chemistry of Fungi. Part XXIV. The Formation of Diquinones.*

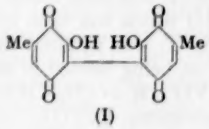
By F. M. Dean, A. M. Osman, and Alexander Robertson.

[Reprint Order No. 5600.]

With hydrogen chloride 2-methoxy-6-*n*-propylquinone † forms the diquinone (XIV) and the dibenzofuran (XV; R = H) in addition to the expected 2-chloro-5-methoxy-3-*n*-propylquinol. The relation between this reaction and the self-condensation of methoxyquinone (Erdtman, *Proc. Roy. Soc.*, 1934, *A*, **143**, 191) is discussed. From results obtained by varying the reaction conditions and by condensing representative quinones with appropriate phenols, a mechanism for the self-condensation has been deduced. The naturally occurring diquinones phoenicin and oosporein are probably not formed by an analogous process.

From the symmetrical nature of the diquinones phoenicin (I), produced by *Penicillium phoenicum* van Beyma and by *P. rubrum* Grasberger and Stroll (Posternak, Ruelius, and Tcherniak, *Helv. Chim. Acta*, 1943, **26**, 2031), and oosporein (II), a metabolite of *Oospora colorans* van Beyma (Kögl and Wessem, *Rec. Trav. chim.*, 1944, **63**, 5), together with the formation of the structurally related benzoquinones fumigatin (III) by *Aspergillus fumigatus* Fresenius (Anslow and Raistrick, *Biochem. J.*, 1938, **32**, 803) and spinulosin (IV) by *A. fumigatus* and by *A. spinulosum* Thom (Raistrick, *Chem. and Ind.*, 1938, **57**, 293) it would appear that the diquinones arise from appropriate mononuclear quinones by some form of coupling reaction.

Methoxyquinone † (VI), which has been isolated recently from fermented wheat germ in which it occurs with 2 : 6-dimethoxyquinone (V) (Cosgrove, Daniels, Whitehead, and Goulden, *J.*, 1952, 4821), has long been known to undergo acid-catalysed coupling to a blue substance which can be oxidised to the diquinone (VII) or reduced to the diquinol (VIII). That the blue substance might either be the quinhydrone of (VII) and (VIII) or have the " indigoid " structure (IX) (Erdtman, *Proc. Roy. Soc.*, 1943, *A*, **143**, 191) does not affect the following discussion. Clearly, linkage to form (VII) occurs in the position alternative to that in phoenicin (I) but, because this difference could be a result of the steric influence of the methyl group, we have examined the corresponding coupling with the relatively accessible compound, 2-methoxy-6-*n*-propylquinone (X; R = H).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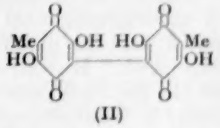
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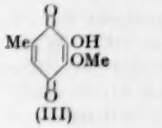
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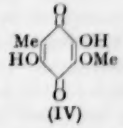
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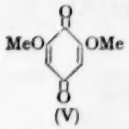
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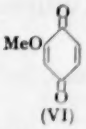
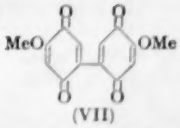

(VI)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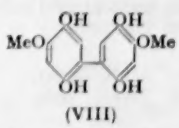
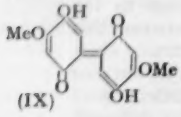

(VIII)

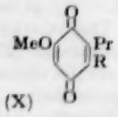
Rearrangement of *O*-allyl-4-nitroguaiacol to 6-allyl-4-nitroguaiacol (XI), followed by catalytic hydrogenation, provided a crude amine, which on oxidation furnished the quinone (X; R = H), but, as the last stage involved strongly acidic media, much of the quinone was destroyed by coupling and the yields were poor. This undesirable feature was avoided by starting with 6-*n*-propylguaiacol, which on persulphate oxidation furnished

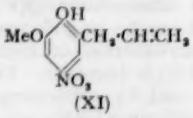
* Part XXIII, *J.*, 1954, 3713.

† Throughout the discussion, the term " quinone " is used for brevity, in place of the systematic 1 : 4-benzoquinone.

2-methoxy-6-*n*-propylquinol (XII; R = H). Controlled oxidation of this quinol then gave excellent yields of the corresponding quinone. Being required for comparison with the hydrogen chloride adduct from the quinone (X; R = H), authentic 2-chloro-5-methoxy-3-*n*-propylquinol (XII; R = Cl) was synthesised from 5-chloroguaiacol. By the Claisen rearrangement of the allyl ether of this phenol and subsequent hydrogenation of the product, 5-chloro-6-*n*-propylguaiacol (XIII) was obtained, which on oxidation furnished 2-chloro-5-methoxy-3-*n*-propylquinone (X; R = Cl) and this was reduced to the quinol (XII; R = Cl).


(IX)


(X)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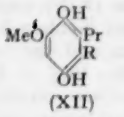
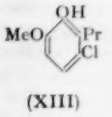
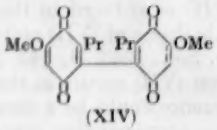
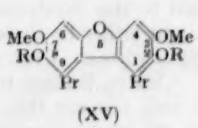

(XII)


(XIII)

But little of the chloroquinol (XII; R = Cl) was formed by the action of hydrogen chloride on 2-methoxy-6-*n*-propylquinone (X; R = H) in chloroform, and the main part of the product was a chlorine-free mixture of the 4 : 4′-dimethoxy-2 : 2′-di-*n*-propyldiquinone (XIV) and, in place of the expected diquinol (XVI), 2 : 8-dihydroxy-3 : 7-dimethoxy-1 : 9-di-*n*-propyldibenzofuran (XV; R = H) (Ring Index no. 1719). This dibenzofuran, which gave a colour reaction with sulphuric acid typical of coumarones, had phenolic properties and formed a diacetate (XV; R = Ac) used for a molecular-weight determination. The oxidation of the dibenzofuran (XV; R = H) to the diquinone (XIV) indicated the relation of the two compounds and this was defined by reduction of the diquinone to the corresponding diquinol (XVI) which regenerated the dibenzofuran (XV; R = H) on dehydration. Cyclisation of the diquinol (XVI) is easily effected with hydrogen chloride, thus accounting for the production of the dibenzofuran instead of the diquinol in the coupling reaction. In contrast, the 4 : 4′-dimethoxydiquinol (VIII) is stable under the same conditions.


(XIV)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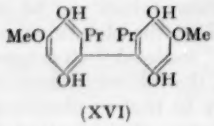
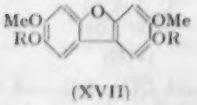

(XVI)

Because the quinone (X; R = H) has two positions at which coupling might occur, the structure (XV; R = Ac) for the diacetate of the dibenzofuran was established by an unambiguous synthesis from the 4 : 4′-dimethoxydiquinol (VIII) which has been oriented by Erdtman (*loc. cit.*). With phosphoric acid the diquinol (VIII) was cyclised to 2 : 8-dihydroxy-3 : 7-dimethoxydibenzofuran (XVII; R = H) and, on being heated in diethylaniline containing a little acetic anhydride, the diallyl ether (XVII; R = CH_2·CH:CH_2) of this supplied 2 : 8-diacetoxy-1 : 9-diallyl-3 : 7-dimethoxydibenzofuran (XVIII) together with an unidentified substance. Hydrogenation of (XVIII) then gave (XV; R = Ac).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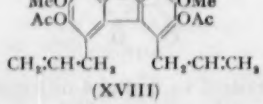
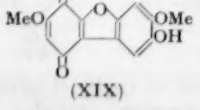
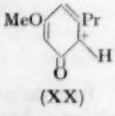

(XVIII)


(XIX)

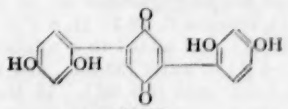

(XX)

Although it was now clear that the propyl groups did not direct orientation in the coupling process, they had other marked effects, of which the relative ease of dehydration of the diquinols has been mentioned. On being heated in 1-bromonaphthalene, the diquinone (VII) is converted into a product to which Erdtman (*Proc. Roy. Soc.*, 1934, *A*, **143**, 223) has allocated structure (XIX), and the stability of the dipropyl analogue (XIV) under similar conditions affords support for this conclusion. It is less easy to see why

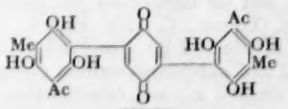
the diquinone (XIV) does not form a hydrogen chloride adduct of the type studied by Lindbergh and his co-workers (*Acta Chem. Scand.*, 1950, **4**, 1192; 1951, **5**, 885). Further, a substance similar to the blue coupled product from methoxyquinone is not formed by the action of acids on the *n*-propylquinone (X; R = H) or by the interaction of solutions of the di-*n*-propyldiquinone (XIV) and the di-*n*-propyldiquinol (XVI) even at −70°. If the blue product is a quinhydrone, the absence of the homologue is only to be expected because a quinhydrone could not be obtained from the parent 2-methoxy-6-*n*-propylquinone (X; R = H). The similar resistance to quinhydrone formation shown by duroquinone disappears at low temperatures (Bothner-By, *J. Amer. Chem. Soc.*, 1951, **73**, 4228) and has been attributed by Michaelis and Granick (*ibid.*, 1944, **66**, 1023) to interaction between the methyl groups in the complex. If, however, the blue product has the alternative structure (IX), the introduction of two *n*-propyl groups *ortho* to the central double bond might well prevent the system from retaining the necessary planar configuration, thus permitting dismutation to the corresponding diquinone and diquinol.

It is usual to consider that the addition of hydrogen chloride to quinones involves a cationic species, here conveniently represented by (XX), which adds chloride ion and then aromatises to the chloroquinol, and it follows that an increased chloride-ion concentration would favour such an addition. When chloroform was replaced by ether, which forms an oxonium chloride with the reagent, the reaction between hydrogen chloride and the *n*-propylquinone (X; R = H) gave a much improved yield of the chloroquinol (X; R = Cl) at the expense of the coupled products.

Because it is acid-catalysed and fails with quinones, *e.g.*, with the chloroquinone (X; R = Cl) or 2-methoxy-5-methylquinone, in which the electron-deficient centres corresponding to that in (XX) are blocked, the coupling process appears to involve the same cationic residue (XX). It is unlikely, however, that the coupled products are formed by the interaction of this cationoid entity (XX) and a second molecule of quinone, which is itself electron-deficient at the point where combination would take place. In view of the formation of the chloroquinol (XII; R = Cl) in the coupling reaction with the *n*-propylquinone the action of hydrogen chloride on methoxyquinone was re-investigated and there was isolated a small quantity of 5-chloro-2-methoxyquinol which appears to have escaped notice hitherto. In the reaction with the quinone (X; R = H) it is reasonable to assume, therefore, that initially the mixture contains, in addition to the chloroquinol (XII; R = Cl), the quinol (XII; R = H) resulting from the action of (XII; R = Cl) on the quinone (X; R = H). This quinol (XII; R = H) would be strongly anionoid at the position appropriate for interaction with (XX), thus leading to the diquinol (XVI) which can then be cyclised to the dibenzofuran (XV; R = H) or be oxidised to the diquinone (XIV). This oxidation could be effected by 2-methoxy-6-*n*-propylquinone or the chloroquinone (X; R = Cl), thereby regenerating 2-methoxy-6-*n*-propylquinol (XII; R = H) required for a fresh cycle. Thus the reaction, once initiated, would continue in the absence of large amounts of the chloroquinol (XII; R = Cl) or of the corresponding quinone. In support of this hypothesis it has been found that the *n*-propylquinol (XII; R = H) and the analogous quinone (X; R = H) interact to give the dibenzofuran (XV; R = H) in yield superior to that obtained in the coupling reaction



(XXI)

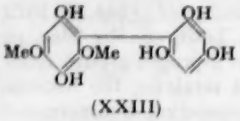


(XXII)

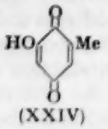
and without the formation of the corresponding diquinone or quinol. Other conditions, *e.g.*, with sulphuric acid in acetic acid, in which coupling has been observed, can be accommodated by variations of the same scheme.

From this argument it appears that non-methoxylated quinones do not couple easily largely because the corresponding quinols are insufficiently anionoid. Nevertheless, quinones of this type would be expected to undergo acid-catalysed condensation with

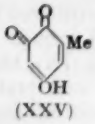
more reactive phenols. Thus Pummerer and Huppman (*Ber.*, 1927, **60**, 1442) obtained the quinhydrone of (XXI) from *p*-benzoquinone and resorcinol in 10% sulphuric acid, and, in the present work, even acetic acid induced a condensation between *p*-benzoquinone and *C*-methylphloracetophenone leading to (XXII) or the related quinol. The inverse state of affairs obtains with 2 : 6-dimethoxyquinone (V), where the reactivity of the cationoid entity is enfeebled by the electromeric effect of the additional methoxyl group. Thus the quinone (V) does not add hydrogen chloride or undergo self-condensation but it does react with the intensely anionoid compound phloroglucinol, giving (XXIII).



(XXIII)



(XXIV)



(XXV)

As similar considerations apply to the coupling of the hydroxyquinone (XXIV) even if this existed in the *o*-quinonoid form (XXV), it seems improbable that the natural diquinones (I) and (II) are formed according to this mechanism or by any simple variation of it.

Experimental

2-Methoxy-6-n-propyl-1 : 4-benzoquinone (X; R = H).—(*a*) A mixture of 4-nitroguaiacol (9·5 g.), potassium carbonate (10 g.), and allyl bromide (6 g.) was heated in boiling acetone (100 ml.) until the orange colour faded. A solution of the product in ether was washed with dilute aqueous sodium hydroxide, dried, and evaporated, leaving an oil which crystallised from light petroleum (b. p. 40—60°), giving *O-allyl-4-nitroguaiacol* in pale yellow rectangular prisms (8 g.), m. p. 53° (Found : 57·7; H, 5·2; N, 6·5. $C_{10}H_{11}O_4N$ requires C, 57·4; H, 5·3; N, 6·7%). This ether (5 g.) was rearranged in boiling quinoline during 30 min. and, after the reaction mixture had been diluted with ether and freed from quinoline by 10% sulphuric acid, the phenolic product was isolated with the aid of 10% aqueous sodium hydroxide. Liberated from the alkaline extracts by dilute hydrochloric acid, *6-allyl-4-nitroguaiacol* (XI) formed yellowish prisms (2 g.), m. p. 72°, from light petroleum (b. p. 40—60°) (Found : C, 57·6; H, 5·2; N, 6·7; OMe, 14·9. $C_9H_8O_3N{\cdot}OMe$ requires C, 57·4; H, 5·3; N, 6·7; OMe, 14·8%). This allylnitroguaiacol (4 g.), dissolved in methanol (100 ml.), was simultaneously hydrogenated and reduced with hydrogen and a 2% palladium–charcoal catalyst in ½ hr. On isolation the crude 4-amino-6-*n*-propylguaiacol was mixed with a solution of ferric sulphate (50 g.) in water (500 ml.), and the oxidation product immediately separated with steam. Extracted with ether from the yellow distillate, *2-methoxy-6-n-propyl-1 : 4-benzoquinone* crystallised from light petroleum (b. p. 40—60°) in yellow rectangular prisms (0·3 g.), m. p. 78—79°, $\lambda_{max.}$ 266 mμ (log ε 4·25), which sublimed easily, were readily soluble in the common organic solvents, and gave a red colour with aqueous sodium hydroxide or concentrated sulphuric acid (Found : C, 66·5; H, 6·63; OMe, 17·0. $C_9H_9O_2{\cdot}OMe$ requires C, 66·7; H, 6·7; OMe, 17·2%).

(*b*) When shaken in methanol (100 ml.) containing 2% palladium–charcoal (1 g.), 6-allylguaiacol (6 g.) (Claisen and Tietze, *Annalen*, 1926, **449**, 81) rapidly absorbed hydrogen (910 ml., *ca.* 1 mol.) and on distillation the product gave 6-n-*propylguaiacol* as an oil (5 g.), b. p. 142°/20 mm. (Found : C, 72·2; H, 8·2. $C_{10}H_{14}O_2$ requires C, 72·3; H, 8·5%).

Sodium nitrite (2·2 g.), dissolved in water (6 ml.), was added to a solution of sulphanilic acid (6·3 g.) and anhydrous sodium carbonate (1·6 g.) in water (30 ml.), and the mixture was poured on ice (3·5 g.) and concentrated hydrochloric acid (6·5 ml.). 15 Minutes later 6-*n*-propylguaiacol (5 g.) in 20% sodium hydroxide (30 ml.) was added to this mixture and next day the resulting dye was reduced *in situ* at 80° with concentrated hydrochloric acid (22 ml.) and stannous chloride (10 g.). The crude aminoguaiacol present in this reaction mixture was oxidised with ferric sulphate (80 g.) in water (500 ml.) to 2-methoxy-6-*n*-propyl-1 : 4-benzoquinone which was isolated by steam-distillation, forming yellow plates, m. p. and mixed m. p. 78—79°. The yield of quinone was very poor.

(*c*) Potassium persulphate (7 g.), in water (250 ml.), was added during 2 hr. to a stirred solution of 6-*n*-propylguaiacol (5 g.) in 10% aqueous sodium hydroxide kept at 10°. 12 Hours

later the red solution was acidified (Congo-red), filtered through cotton wool to remove tar, acidified to litmus, and kept at 100° for 1 hr. From the brown resinous product, which was isolated with ether, boiling light petroleum (b. p. 80—100°) extracted *2-methoxy-6-n-propylquinol* (XII; R = H), forming needles (1·5 g.), m. p. 106°, easily soluble in organic solvents except light petroleum and readily soluble in aqueous sodium hydroxide (Found: C, 66·0; H, 7·5; OMe, 17·1. $C_9H_{11}O_2$·OMe requires C, 65·9; H, 7·7; OMe, 17·0%). Oxidation of this quinol (6 g.) in 10% acetic acid (30 ml.) with 2% aqueous chromic acid (100 ml.) at 0° during ½ hr. gave an almost quantitative yield of 2-methoxy-6-*n*-propyl-1 : 4-benzoquinone, m. p. and mixed m. p. 78—79°.

5-Chloro-6-n-propylguaiacol (XIII).—The product from the interaction of 5-chloroguaiacol (6·0 g.) (Jona and Pozzi, *Gazzetta*, 1911, **41**, I, 722), potassium carbonate (6 g.), and allyl bromide (5·5 g.) in acetone (100 ml.) on the steam-bath for 4 hr. was isolated in the usual way and on distillation gave *O-allyl-5-chloroguaiacol* (5 g.), b. p. 142°/20 mm. (Found: OMe, 15·4. C_9H_8OCl·OMe requires OMe, 15·6%). On being boiled with dimethylaniline (4 g.) for 1 hr., this ether (4·5 g.) was completely isomerised. The cooled reaction mixture was diluted with ether, freed from the base with dilute sulphuric acid, dried (Na_2SO_4), and evaporated, leaving *6-allyl-5-chloroguaiacol* as an oil (3·7 g.), b. p. 150°/20 mm. (Found: C, 60·2; H, 5·4; OMe, 15·3. C_9H_8OCl·OMe requires C, 60·5; H, 5·5; OMe, 15·6%). The *benzoate* separated from methanol in plates, m. p. 78° (Found: C, 67·3; H, 5·1; OMe, 10·3. $C_{16}H_{13}O_2Cl$·OMe requires C, 67·2; H, 4·9; OMe, 10·2%). The allylguaiacol (8 g.) in methanol (30 ml.) containing 0·5% palladium–charcoal (2 g.) was allowed to absorb one mol. (895 ml.) of hydrogen (*ca.* 10 min.). Evaporation of the filtered solution and distillation of the residue furnished *5-chloro-6-n-propylguaiacol* as an oil (7·5 g.), b. p. 156°/20 mm. (Found: C, 59·7; H, 6·3. $C_{10}H_{13}O_2Cl$ requires C, 59·9; H, 6·5%), giving a *benzoate* which separated from dilute alcohol in needles, m. p. 100° (Found: OMe, 10·3. $C_{16}H_{14}O_2Cl$·OMe requires OMe, 10·2%).

2-Chloro-5-methoxy-3-n-propylquinol (XII; R = Cl).—This quinol was prepared by the method (*b*) employed for 2-methoxy-6-*n*-propylquinone. 5-Chloro-6-*n*-propylguaiacol (4 g.) in 10% aqueous sodium hydroxide (50 ml.) at 0° was mixed with diazotised sulphanilic acid (6 g.). Next day the solution was treated with concentrated hydrochloric acid (22 ml.) and stannous chloride (10 g.), and then heated at 90° until the colour changed to brown before oxidation with ferric sulphate (80 g.). After isolation by steam-distillation followed by extraction with ether the greenish resinous product was crystallised from light petroleum (b. p. 40—60°), giving *2-chloro-5-methoxy-3-n-propyl-1 : 4-benzoquinone* (X; R = Cl) in greenish-yellow rectangular prisms (2·0 g.), m. p. 92°, which readily sublimed and formed a pink solution in alkali and a red one in concentrated sulphuric acid (Found: C, 56·2; H, 5·3; Cl, 16·3; OMe, 14·3. $C_9H_8O_2Cl$·OMe requires C, 55·9; H, 5·1; Cl, 16·6; OMe, 14·5%). This quinone (1 g.), suspended in water (50 ml.), was treated with sulphur dioxide until no further change was apparent and the white precipitate then collected, dried, and purified from light petroleum (b. p. 60—80°), giving *2-chloro-5-methoxy-3-n-propylquinol* in colourless prisms (0·8 g.), m. p. 103—104°, which, on oxidation with chromic acid in acetic acid, regenerated the parent quinone (Found: C, 55·8; H, 6·2; Cl, 16·1; OMe, 14·2. $C_9H_{10}O_2Cl$·OMe requires C, 55·4; H, 6·0; Cl, 16·4; OMe, 14·3%).

2 : 8-Diallyloxy-3 : 7-dimethoxydibenzofuran (XVII; R = CH_2·CH:CH_2).—The blue coupled product (10 g.) from methoxyquinone was heated under reflux with zinc dust (2 g.) in 55% acetic acid (200 ml.) until the blue colour disappeared (*ca.* 20 min.), and after the addition of 2N-hydrochloric acid (5 ml.) the hot solution was filtered immediately. On cooling, the filtrate deposited fawn prisms (7·2 g.), m. p. 210° (decomp.), of *2 : 5 : 2′ : 5′-tetrahydroxy-4 : 4′-dimethoxydiphenyl*, the properties of which agreed exactly with those reported by Erdtman (*Proc. Roy. Soc.*, 1934, *A*, **143**, 191). When sifted into syrupy phosphoric acid (25 ml.) at 180°, this quinol (4 g.) at once gave a blue solution which on cooling deposited lilac crystals. After being diluted with an equal volume of water, the mixture was filtered and the solid was washed with much water and crystallised from alcohol or benzene–light petroleum (b. p. 60—80°) giving *2 : 8-dihydroxy-3 : 7-dimethoxydibenzofuran* (XVII; R = H) in colourless plates, m. p. 188°, $\lambda_{max.}$ 316 mμ (log ε 4·4), which gave an intense blue concentrated sulphuric acid reaction [Found: C, 64·8; H, 4·5; OMe, 23·8. $C_{12}H_8O_3(OMe)_2$ requires C, 64·6; H, 4·7; OMe, 24·0%]. The *diacetate* separated from dilute alcohol in needles, m. p. 200° [Found: C, 63·0; H, 4·7; OMe, 18·2. $C_{16}H_{10}O_5(OMe)_2$ requires C, 6·28; H, 4·7; OMe, 18·2%]. Prepared from this dihydroxydibenzofuran (2 g.), potassium carbonate (2 g.), and allyl bromide (1·6 ml.) in refluxing acetone (200 ml.) during 6 hr. and recrystallised from dilute alcohol, *2 : 8-diallyloxy-3 : 7-dimethoxydibenzofuran* formed flat needles (1·5 g.), m. p. 112—113°,

insoluble in alkalis and giving a deep blue sulphuric acid reaction (Found : C, 70·6; H, 6·2. $C_{29}H_{30}O_5$ requires C, 70·6; H, 5·9%).

2 : 8-*Diacetoxy*-3 : 7-*dimethoxy*-1 : 9-*di*-n-*propyldibenzofuran* (XV; R = Ac).—A mixture of 2 : 8-diallyloxy-3 : 7-dimethoxydibenzofuran (5 g.), diethylaniline (40 ml.), and acetic anhydride (5 ml.) in nitrogen was heated (oil-bath at 180—190°) for 5 hr., cooled, diluted with ether (200 ml.), and filtered. Freed from diethylaniline by hydrochloric acid, the filtrate was evaporated, leaving a yellow gum which solidified on trituration with methanol. The solid (5 g.) appeared to be a complex mixture from which two compounds were isolated by fractional crystallisation from alcohol and ethyl acetate alternately. The less soluble *substance* formed prisms (0·5 g.), m. p. 220°, from alcohol having a blue sulphuric acid reaction and resisting hydrogenation under mild conditions (Found : C, 66·9; H, 6·3; OMe, 14·8%). Purified from alcohol, the more soluble fraction gave 2 : 8-*diacetoxy*-1 : 9-*diallyl*-3 : 7-*dimethoxydibenzofuran* in prisms (1·8 g.), m. p. 166°, with a blue sulphuric acid reaction [Found : C, 67·8; H, 6·0; OMe, 15·1. $C_{22}H_{16}O_5(OMe)_2$ requires C, 67·9; H, 5·7; OMe, 14·6%]. Hydrogenated with a 2% palladium–charcoal catalyst (0·5 g.) in alcohol (200 ml.), this diallyldibenzofuran (0·5 g.) absorbed 2 mols. of hydrogen in 5 min. and on isolation the resulting 2 : 8-*diacetoxy*-3 : 7-*dimethoxy*-1 : 9-*di*-n-*propyldibenzofuran* separated from alcohol in squat prisms (0·5 g.), m. p. 169°, having a blue sulphuric acid reaction [Found : C, 67·1; H, 6·7%; *M* (Rast), 405. $C_{34}H_{38}O_7$ requires C, 67·3; H, 6·5%; *M*, 428].

Action of Hydrogen Chloride on 2-*Methoxy*-6-n-*propyl*-1 : 4-*benzoquinone*.—Hydrogen chloride was led into a solution of the quinone (2 g.) in chloroform (50 ml.) for 1 hr. and the solvent removed in a vacuum, leaving a brown residue which solidified. This was triturated with a little methanol to remove resin, together with a very small quantity of 2-chloro-5-methoxy-3-*n*-propylquinol (XII; R = Cl) which separated from boiling light petroleum (b. p. 40—60°) in prisms, m. p. and mixed m. p. 103°. Fractional crystallisation of the main residual product from methanol gave a less soluble fraction of 4 : 4′-*dimethoxy*-6 : 6′-*di*-n-*propyldiphenyl*-2 : 5-2′ : 5′-*diquinone* (XIV) which on repeated purification from the same solvent formed yellow hexagonal prisms (0·6 g.), m. p. 172°, $\lambda_{max.}$ 272 mμ (log ε 4·3), subliming unchanged at 180° (bath)/0·001 mm., and giving an orange colour with sulphuric acid and a pink with aqueous sodium hydroxide [Found : C, 67·2; H, 6·2; OMe, 17·1. $C_{18}H_{16}O_4(OMe)_2$ requires C, 67·0; H, 6·1; OMe, 17·3%]. Recrystallised from dilute methanol, the more soluble fraction gave 2 : 8-*dihydroxy*-3 : 7-*dimethoxy*-1 : 9-*di*-n-*propyldibenzofuran* (XV; R = H) in rectangular plates (0·7 g.), m. p. 152°, $\lambda_{max.}$ 227, 312 mμ (log ε 4·6, 4·45), subliming unchanged at 170° (bath)/0·001 mm., soluble in aqueous sodium hydroxide but not in aqueous sodium carbonate, and giving a deep blue sulphuric acid reaction [Found : C, 69·8; H, 7·0; OMe, 17·8. $C_{18}H_{16}O_3(OMe)_2$ requires C, 69·8; H, 6·9; OMe, 18·0%]. The diacetate (XV; R = Ac) was identical with an authentic specimen, m. p. and mixed m. p. 169°.

When the chloroform was replaced by ether in the foregoing experiment there was formed a crude solid which on fractional crystallisation from methanol gave three products. The least soluble fraction was the diquinone (0·4 g.), m. p. and mixed m. p. 172°, the middle fractions consisted chiefly of the dibenzofuran (0·5 g.), m. p. and mixed m. p. 152° on purification, and the most soluble material, isolated by dilution with water, was 2-chloro-5-methoxy-3-*n*-propylquinol (0·6 g.), m. p. and mixed m. p. 103—104°.

Interconversion of the Diquinone (XIV) *and the Corresponding Dibenzofuran* (XV; R = H).—The dibenzofuran (XV; R = H) (0·5 g.) in boiling alcohol (15 ml.) was treated with ferric chloride (1 g.) for 30 min. and the solution diluted with ether, thoroughly washed with water, dried, and evaporated, leaving 4 : 4′-dimethoxy-6 : 6′-di-*n*-propyldiphenyl-2 : 5-2′ : 5′-diquinone (0·25 g.), m. p. and mixed m. p. 172°.

The diquinone (0·5 g.) suspended in water (20 ml.) containing methanol (5 ml.), was reduced by sulphur dioxide in 20 min. The white precipitate was collected, washed with water, and crystallised from dilute methanol, giving 3 : 6 : 3′ : 6′-*tetrahydroxy*-4 : 4′-*dimethoxy*-2 : 2′-*di*-n-*propyldiphenyl* (XVI) in prisms (0·45 g.), m. p. 190°, which were easily oxidised in air and gave a red solution in aqueous sodium hydroxide and an emerald-green sulphuric acid reaction (Found : C, 66·2; H, 7·2. $C_{20}H_{26}O_6$ requires C, 66·3; H, 7·2%). The *tetra-acetate* separated from dilute alcohol in plates or prisms, m. p. 160°, $\lambda_{max.}$ 280 mμ (log ε 3·6) (Found : C, 63·3; H, 6·6. $C_{28}H_{34}O_{10}$ requires C, 63·4; H, 6·5%). The dibenzofuran (XV; R = H) (0·15 g.), which sublimed from an intimate mixture of the diquinol (0·2 g.) and phosphoric oxide (0·5 g.) kept at 190°/0·05 mm., was produced in the same yield when the diquinol in chloroform was treated with hydrogen chloride at 0° for 1 hr., and was identified by comparison with an authentic specimen.

Action of Hydrogen Chloride on Methoxy-1 : 4-benzoquinone.—Methoxy-1 : 4-benzoquinone was stable in dilute acetic acid or even in dilute (<1%) mineral acids. 2N-Mineral acids caused immediate coupling (cf. Erdtman, *loc. cit.*).

The methoxyquinone (1 g.) in ice-cold chloroform (25 ml.) was treated with a stream of hydrogen chloride for 5 min. and the blue precipitate (0·95 g.) collected and identified with the product prepared according to the directions of Erdtman (*loc cit.*). The residue left on evaporation of the chloroform liquor was extracted with boiling light petroleum (b. p. 40—60°). The extracts were cooled, and, after removal of a little insoluble blue compound, concentrated, and chilled. The resulting crystalline precipitate was purified from the same solvent, giving a small amount of 2-chloro-5-methoxyquinol, m. p. 128°, undepressed on admixture with an authentic specimen (Asp and Lindbergh, *Acta Chem. Scand.*, 1950, **4**, 60).

Condensation of 2-Methoxy-6-n-propylquinol with 2-Methoxy-6-n-propyl-1 : 4-benzoquinone.—A slow stream of hydrogen chloride was led into a solution of the quinone (50 mg.) and the quinol (50 mg.) in chloroform (5 ml.). An hour later the solution was evaporated and the residue was thoroughly extracted with boiling light petroleum (b. p. 60—80°). On cooling, the concentrated extracts deposited a reddish mass (70 mg.) of 2 : 8-dihydroxy-3 : 7-dimethoxy-1 : 9-di-*n*-propyldibenzofuran (XV; R = H), forming colourless plates, m. p. and mixed m. p. 152°, from methanol.

2 : 5-Di-(3-acetyl-2 : 4 : 6-trihydroxy-5-methylphenyl)-1 : 4-benzoquinone (*3 : 3″-Diacetyl-2 : 4 : 6 : 2″ : 4″ : 6″-hexahydroxy-5 : 5″-dimethyl-*p*-terphenyl-2′ : 5′-quinone*) (XXII).—A solution of *p*-benzoquinone (1·1 g.) in acetic acid (30 ml.), containing powdered *C*-methylphloracetophenone (0·9 g.), was vigorously stirred for 24 hr. and the solid product isolated, dried in air, and washed with cold methanol, leaving the *quinone* (XXII) as bright yellow prisms (0·8 g.), m. p. 245° (decomp.) after blackening at 190°, insoluble in alcohol, dioxan, chloroform, or ethyl acetate and decomposing in warm acetic acid (Found : C, 61·5; H, 4·6. $C_{24}H_{20}O_{10}$ requires C, 61·5; H, 4·3%). In aqueous sodium carbonate this quinone gave a green, and in 2N-aqueous sodium hydroxide a red, solution; the sulphuric acid reaction was deep greenish-red, changing to purple and finally inky-blue on warming. The methanolic washings of the quinone were concentrated, giving quinhydrone in glistening green-black crystals (0·2 g.), m. p. 171° (decomp.).

2 : 5-Di-(3-acetyl-2 : 4 : 6-trihydroxy-5-methylphenyl)quinol (*3 : 3″-Diacetyl-2 : 4 : 6 : 3′ : 5′ : 2″ : 4″ : 6″-octahydroxy-5 : 5″-dimethyl-*p*-terphenyl*).—(*a*) A stirred solution of *p*-benzoquinone (0·55 g.) in acetic acid (10 ml.), containing *C*-methylphloracetophenone (0·9 g.), was kept at 60° for 1 hr. The mixture became red and the nature of the solid changed. Next day the pink solid was collected, washed with acetic acid and then ether, and dried, giving *2 : 5-di-(3-acetyl-2 : 4 : 6-trihydroxy-5-methylphenyl)quinol* in prisms (0·85 g.), m. p. 270° (decomp.) (Found : C, 61·7; H, 5·0. $C_{24}H_{22}O_{10}$ requires C, 6·16; H, 4·7%). This quinol, which is soluble in alcohol, gave a transient green-brown ferric reaction, a brilliant red solution in 2N-aqueous sodium hydroxide, and a rose-red warm sulphuric acid reaction. With the corresponding quinone it appeared to form a dark red quinhydrone which could not be satisfactorily characterised.

(*b*) Sodium hydrogen sulphite (0·3 g.) was added to the quinone (XXIII) (0·3 g.) suspended in acetic acid (4 ml.) and water (1 ml.). The mixture was warmed gently and further small amounts of sulphite were added until the yellow colour of the mixture faded. The precipitate of the quinol was collected, washed thoroughly with hot distilled water, and crystallised from acetic acid, forming cream prisms (0·24 g.), m. p. 267° (decomp.), having the same colour reactions as the compound obtained by method (*a*) (Found : C, 61·5; H, 5·0%).

3 : 6 : 2′ : 4′ : 6′-Pentahydroxy-2 : 4-dimethoxydiphenyl (XXIII).—An intimate mixture of anhydrous phloroglucinol (1·3 g.) and 2 : 6-dimethoxy-1 : 4-benzoquinone (1·7 g.) was moistened with acetic acid and warmed, giving a dark solution from which, 15 minutes later, a solid separated on cooling. A pure product was not obtained from this but the mother liquor slowly deposited a white solid which on crystallisation from water furnished *3 : 6 : 2′ : 4′ : 6′-pentahydroxy-2 : 4-dimethoxydiphenyl* in prisms, m. p. 250° (decomp.), with a negative ferric reaction in water [Found : C, 53·3; H, 5·6; OMe, 19·3, 19·5. $C_{12}H_8O_5(OMe)_2.H_2O$ requires C, 53·8; H, 5·2; OMe, 19·9%]. Attempted recrystallisation of this phenol from acetic acid caused partial decomposition. On being warmed, the lilac solution of the compound in concentrated sulphuric acid became green and then purple.

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The Bromination of o- *and* p-*Hydroxyaryl Ketones.*

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2-Hydroxyacetophenone, 2-hydroxypropiophenone, and similar ketones, like their *p*-isomers, undergo predominantly side-chain substitution with bromine in anhydrous acetic acid and nuclear substitution in aqueous acetic acid. However, hydroxyaryl ketones of high molecular weight, such as 4-hydroxystearophenone, polyhydroxy-ketones, such as respropiophenone, and hydroxynaphthyl ketones, such as 2- and 4-acetyl-1-naphthol, undergo only nuclear monobromination.

It has generally been assumed that hydroxyaryl ketones undergo nuclear substitution with free bromine, and that side-chain bromination occurs only when the positions *ortho* and *para* to the hydroxy-groups are blocked. However, it was recently found (Buu-Hoï, Xuong, and Lavit, *J.*, 1954, 1034) that 4-hydroxy-acetophenone and -propiophenone underwent side-chain bromination in anhydrous acetic acid, and nuclear bromination in aqueous acetic acid. These studies have now been extended to other hydroxy-ketones.

With 1 mol. of bromine, 2-hydroxy-acetophenone and -propiophenone gave ω-bromo-2-hydroxyacetophenone and α-bromo-2-hydroxypropiophenone in anhydrous acetic acid; in aqueous acetic acid, 5-bromo-2-hydroxy-acetophenone and -propiophenone were obtained. Yields in these and similar side-chain brominations were far from quantitative, but, although nuclear substitution may have occurred to a small extent, no such product could be isolated. Further substitution affected the nucleus in both solvents, as shown by the formation of 3 : 5-dibromo-2-hydroxypropiophenone from 2-hydroxypropiophenone and 2 mols. of bromine in aqueous acetic acid, and of α : 5-dibromo-2-hydroxypropiophenone in anhydrous acetic acid; 2-hydroxyacetophenone gave similar results. The same behaviour was observed with 5-fluoro-2-hydroxypropiophenone, which was monobrominated in the side-chain in anhydrous acetic acid, and with 2-hydroxy-5-methylacetophenone, which gave ω- or 3-bromo- or 3 : ω-dibromo-2-hydroxy-5-methylacetophenone according to the experimental conditions.

With hydroxy-ketones derived from higher fatty acids, no side-chain bromination occurred, probably on account of steric hindrance (cf. Buu-Hoï *et al.*, *Rec. Trav. chim.*, 1947, **66**, 308; *J.*, 1946, 795; 1948, 106); 4-hydroxystearophenone, for instance, gave the 3-bromo-derivative with 1 mol. of bromine, and the 3 : 5-dibromo-derivative with 2 mols. in anhydrous or aqueous acetic acid. Further, respropiophenone (2 : 4-dihydroxypropiophenone) gave the 3 : 5-dibromo-derivative with 1 or 2 mols. of bromine in either solvent; and in confirmation of Hantzsch's finding (*Ber.*, 1906, **39**, 3097), monobromination of 2-acetyl-1-naphthol in anhydrous acetic acid afforded the 4-bromo-naphthol, and dibromination yielded the 4 : ω-dibromo-compound (Fries and Frellstedt, *Ber.*, 1921, **54**, 720). 4-Acetyl-1-naphthol similarly gave 4-acetyl-2-bromo-1-naphthol with 1 mol. of bromine.

The selective nuclear brominations in aqueous acetic acid observed here are in line with the observations of Robertson *et al.* (*J.*, 1943, 276, 279; 1947, 1167; 1948, 100; 1949, 294, 933) that the rates of aromatic halogenation are very much increased by the presence of water, and that "ionisation of the halogen–halogen bond occurs during, rather than before, association with the aromatic nucleus" (cf. Braude, *Ann. Reports*, 1949, **46**, 138). Throughout the present work, nuclear was much faster than side-chain bromination.

Structures of the ω-bromo-ketones were proved by conversion into coumaranones by mild alkali (Friedländer and Neudörfer, *Ber.*, 1897, **30**, 1081; Fries *et al.*, *Ber.*, 1908, **41**, 4278; 1910, **43**, 215), or more conveniently by Hinsberg reactions (*Annalen*, 1896, **292**, 246; Buu-Hoï and Khôi, *Bull. Soc. chim.*, 1950, **17**, 753) with *o*-phenylenediamine to give 2-hydroxyarylquinoxalines.

Experimental

ω-Bromo-2-hydroxyacetophenone.—To a solution of *o*-hydroxyacetophenone (16 g.; prepared by Fries rearrangement of phenyl acetate) in glacial acetic acid (200 c.c.), a solution of bromine (18·5 g.) in the same solvent (50 c.c.) was added dropwise (3 hr.) with shaking; after decolor-

ation, the solution was diluted with water and the oil taken up in chloroform, washed, and dried (Na_2SO_4); the solvent was evaporated and the residue fractionated *in vacuo*; the *bromo-ketone* (12 g.), b. p. 152—158°/18 mm., n_D^{25} 1·6168, formed yellowish needles, m. p. 45°, from light petroleum (Found: C, 44·5; H, 3·5. $C_8H_7O_2Br$ requires C, 44·7; H, 3·3%). The constitution was determined by 2 hours' refluxing of this ketone (2 g.) and sodium acetate (2 g.) in ethanol (30 c.c.); the precipitate of coumaranone formed on dilution with water crystallised as pale yellow needles, m. p. 101°, from methanol (lit., m. p. 101—102°). The forerun from the bromination product consisted of *o*-hydroxyacetophenone, and recrystallisation of the higher-boiling fraction gave ω : 5-*dibromo*-2-*hydroxyacetophenone* (0·5 g.), yellowish prisms, m. p. 107°, from acetic acid (Found: C, 32·8; H, 2·3. $C_8H_6O_2Br_2$ requires C, 32·7; H, 2·0%); the same compound was obtained in almost theoretical yield from bromine (1 mol.) and either ω-bromo-2-hydroxyacetophenone in 50% aqueous acetic acid, or 5-bromo-2-hydroxyacetophenone in glacial acetic acid.

ω-Bromo-2-hydroxyacetophenone (3 g.), *o*-phenylenediamine (1·5 g.), and sodium acetate (2 g.) in ethanol (50 c.c.) were refluxed for 2 hr.; the precipitate of 2-*o*-*hydroxyphenylquinoxaline* obtained on cooling formed orange-yellow, sublimable needles (3 g.), m. p. 191°, from ethanol (Found: C, 75·4; H, 4·5; N, 12·4. $C_{14}H_{10}ON_2$ requires C, 75·7; H, 4·5; N, 12·6%).

Nuclear Bromination of o-*Hydroxyacetophenone.*—(*a*) To a solution of this ketone (5 g.) in 50% aqueous acetic acid (50 c.c.), bromine (5·8 g.) in 80% aqueous acetic acid (25 c.c.) was added in small portions with shaking. The oil formed on dilution with water was taken up in chloroform, washed with water, dried (Na_2SO_4), and purified by vacuum-distillation, giving 5-bromo-2-hydroxyacetophenone (5 g.), b. p. 145—148°/20 mm., which formed colourless needles, m. p. 62° (Found: Br, 37·3. Calc. for $C_8H_7O_2Br$: Br, 37·2%); Kostanecki and Ludwig (*Ber.*, 1898, **31**, 2953) gave m. p. 61—62°.

(*b*) A solution of *o*-hydroxyacetophenone (3 g.) in 50% aqueous acetic acid (50 c.c.) was treated with bromine (7 g.), dissolved in 80% aqueous acetic acid, in small portions. The mixture was then heated at 65° to decoloration, water was added, and the solid precipitate recrystallised from aqueous acetic acid; 3 : 5-*dibromo*-2-*hydroxyacetophenone* formed pale yellow needles (4 g.), m. p. 111° (Found: Br, 54·1. $C_8H_6O_2Br_2$ requires Br, 54·4%).

Bromination of o-*Hydroxypropiophenone.*—(*a*) *o*-Hydroxypropiophenone (10 g.; n_D^{25} 1·550) in 65% aqueous acetic acid (150 c.c.) was treated with bromine (10·7 g.), dissolved in 80% aqueous acetic acid, at room temperature; 5-*bromo*-2-*hydroxypropiophenone*, obtained on dilution with water, crystallised as yellowish needles (10 g.), m. p. 77°, from methanol (Found: C, 47·5; H, 3·8. $C_9H_9O_2Br$ requires C, 47·2; H, 3·9%).

(*b*) *o*-Hydroxypropiophenone (10 g.) in anhydrous acetic acid (140 c.c.) was cooled in ice-water and treated dropwise (2 hr.) with bromine (10·6 g.) in the same solvent; the oil formed on dilution with water was taken up in chloroform and vacuum-distilled, giving α-*bromo*-2-*hydroxypropiophenone* as a pale yellow, lachrymatory oil (6 g.), b. p. 145—150°/15 mm., $n_D^{22.5}$ 1·5930 (Found: C, 47·0; H, 3·8%). Its constitution was determined by removal of bromine with hot aniline and conversion into 2-methylcoumaranone, b. p. 122°/16 mm., n_D^{25} 1·5650, by sodium acetate in hot ethanol [Störmer and Atenstädt (*Ber.*, 1902, **35**, 3565) gave b. p. 163—165°/40 mm.; von Auwers (*Ber.*, 1919, **52**, 121; *Annalen*, 1912, **393**, 360) gave $n_D^{19·7}$ 1·5630, b. p. 119°/15—16 mm.].

(*c*) *o*-Hydroxypropiophenone (10 g.) in 65% aqueous acetic acid (150 c.c.) with bromine (21·4 g.) in 80% aqueous acetic acid yielded 3 : 5-*dibromo*-2-*hydroxypropiophenone* (11 g.), pale yellow needles, m. p. 118° (from methanol) (Found: C, 35·0; H, 2·8. $C_9H_8O_2Br_2$ requires C, 35·1; H, 2·6%).

(*d*) Bromination (2 mols. of halogen) in anhydrous acetic acid gave 5 : α-*dibromo*-2-*hydroxypropiophenone* (10 g.), yellowish prisms, m. p. 99° (from ethanol) (Found: C, 34·7; H, 2·7%); the same compound was obtained on monobromination of 5-bromo-2-hydroxypropiophenone in anhydrous acetic acid. The presence of a labile bromine atom was shown by the formation of aniline hydrobromide with hot aniline.

α-*Bromo*-5-*fluoro*-2-*hydroxypropiophenone.*—5-Fluoro-2-hydroxypropiophenone (6·5 g.) with bromine (6·2 g.) in anhydrous acetic acid (100 c.c.) gave a *bromo-compound* (5 g.), b. p. 147°/16 mm., n_D^{26} 1·5748, yellowish prisms, m. p. 48° (from light petroleum) (Found: C, 43·4; H, 3·2. $C_9H_8O_2BrF$ requires C, 43·7; H, 3·2%).

Bromination of 4-*Hydroxystearophenone.*—(*a*) The ketone (2·5 g.) in anhydrous acetic acid (350 c.c.) with bromine (1·1 g.) gave 3-*bromo*-4-*hydroxystearophenone* (2·5 g.), colourless needles, m. p. 96° (from aqueous acetic acid) (Found: C, 65·2; H, 8·9. $C_{24}H_{39}O_2Br$ requires C, 65·6; H, 8·9%).

(*b*) Similar treatment with double the amount of bromine yielded 3 : *5-dibromo-4-hydroxystearophenone* (3 g.), colourless leaflets, m. p. 80° (from acetic acid) (Found : C, 55·3; H, 7·3. $C_{24}H_{38}O_2Br_2$ requires C, 55·6; H, 7·3%). The same compound was obtained by bromination in aqueous acetic acid.

Bromination of 2-Hydroxy-5-methylacetophenone.—(*a*) 2-Hydroxy-5-methylacetophenone (20 g.) in anhydrous acetic acid was treated with bromine (21·3 g.); after 7 hr., water was added, and the product taken up in chloroform and purified by vacuum-distillation. *ω-Bromo-2-hydroxy-5-methylacetophenone* (12 g.) was formed as a pale yellow, lachrymatory oil, n_D^{25} 1·6023 (Found : C, 46·9; H, 3·7. $C_9H_9O_2Br$ requires C, 47·2; H, 3·9%). This compound (5 g.) with *o*-phenylenediamine (2·4 g.) and sodium acetate (3 g.) in ethanol (50 c.c.), refluxed for 2 hr., gave 2-(*2-hydroxy-5-methylphenyl*)*quinoxaline* (4 g.), yellow, sublimable needles, m. p. 198° (from ethanol) (Found : C, 76·0; H, 5·2. $C_{15}H_{12}ON_2$ requires C, 76·3; H, 5·1%).

(*b*) The ketone (10 g.) in 50% aqueous acetic acid (120 c.c.) with bromine (10·6 g.) in 80% aqueous acetic acid gave 3-*bromo-2-hydroxy-5-methylacetophenone* (10 g.), yellowish needles (from methanol), m. p. 89° (Found : C, 47·0; H, 4·0%).

3 : *ω-Dibromo-2-hydroxy-5-methylacetophenone.*—Obtained by treating ω-bromo-2-hydroxy-5-methylacetophenone (3·7 g.) in 50% aqueous acetic acid at 60° with bromine (2·6 g.; 75% yield), or 2-hydroxy-5-methylacetophenone (5 g.) in anhydrous acetic acid with bromine (10·6 g.; 55% yield), this *ketone* crystallised as pale yellow needles, m. p. 106°, from aqueous acetic acid (Found : C, 34·8; H, 2·7. $C_9H_8O_2Br_2$ requires C, 35·1; H, 2·6%).

This ketone (3 g.), *o*-phenylenediamine (1 g.), and sodium acetate (1·3 g.) in ethanol (70 c.c.) were refluxed for 3 hr. The precipitate gave on recrystallisation from benzene 2-(*3-bromo-2-hydroxy-5-methylphenyl*)*quinoxaline* (2 g.) as yellow, sublimable needles, m. p. 232° (Found : C, 57·0; H, 3·3; N, 8·6. $C_{15}H_{11}ON_2Br$ requires C, 57·1; H, 3·5; N, 8·9%). When refluxing was for only 30 min., a meriquinonoid compound was obtained, which crystallised as orange-red needles, m. p. 206°, from benzene, and underwent oxidation to the foregoing quinoxaline above its m. p.

Bromination of 2 : 4-*Dihydroxypropiophenone.*—The ketone (1 g.) in 50% aqueous acetic acid was treated with bromine (1 or 2 g.) in the usual way. 3 : 5-Dibromo-2 : 4-dihydroxypropiophenone formed colourless needles, m. p. 158°, from aqueous acetic acid (Found : Br, 49·6. Calc. for $C_9H_8O_3Br_2$: Br, 49·4%); Gnagy (*J. Amer. Chem. Soc.*, 1923, **45**, 807) gave m. p. 148°. The same compound was obtained by bromination in anhydrous acetic acid, and some α-bromo-compound, reacting with *o*-phenylenediamine, was detected, but no attempt was made to isolate it.

Bromination of 2-Acetyl-1-naphthol.—Reaction with 2 mols. of bromine in anhydrous acetic acid gave 4-bromo-2-bromoacetyl-1-naphthol (75%), m. p. 148°; Fries and Frellstedt (*loc. cit.*) gave m. p. 147°. Condensation of this ketone (2·25 g.) with *o*-phenylenediamine (0·7 g.) in the presence of sodium acetate (1 g.) gave 2-(*4-bromo-1-hydroxy-2-naphthyl*)*quinoxaline* (2 g.), ochre-yellow needles, m. p. 259° (decomp. >250°) (Found : C, 61·1; H, 3·2. $C_{18}H_{11}ON_2Br$ requires C, 61·5; H, 3·2%).

Bromination of 4-Acetyl-1-naphthol.—4-Acetyl-1-naphthol (5 g.; prepared by demethylation of 4-acetyl-1-methoxynaphthalene with pyridine hydrochloride) in anhydrous acetic acid (300 c.c.) with bromine (4·3 g.) gave the *2-bromo-derivative* (5 g.), as colourless needles, m. p. 136° (from acetic acid) (Found : C, 54·0; H, 3·5. $C_{12}H_9O_2Br$ requires C, 54·3; H, 3·4%); the same compound was obtained by bromination in 50% aqueous acetic acid, and contained no labile bromine (aniline test).

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Thiophen Derivatives of Biological Interest. Part IX. Odour and Chemical Structure in the Thiophen Series.*

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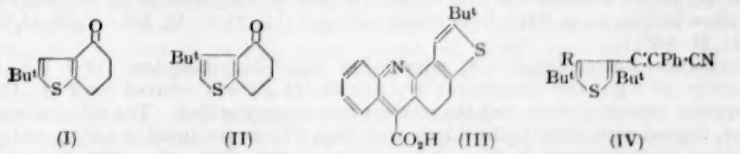
The relation between odour and chemical constitution in thiophen compounds has been investigated. 2- and 3-*tert.*-Butyl-4 : 5 : 6 : 7-tetrahydro-4-oxothionaphthen were synthesised from 2- and 3-*tert.*-butylthiophen by the succinic anhydride method; their vapours have an odour reminiscent of 7-*tert.*-butyl-1-tetralone; 5-*iso*propyl-2-thenaldehyde, 2-2′-thienylideneheptanal, and a series of esters of 2-thenoic acid have odours similar to those of the benzene isologues. Other reactions of 3-*tert.*-butylthiophen and 2 : 5-di-*tert.*-butylthiophen were investigated.

7-*tert.*-Butyl-1-tetralone has an odour reminiscent of smouldering sandalwood (Buu-Hoï and Cagniant, *Compt. rend.*, 1942, **214**, 115; Cagniant and Buu-Hoï, *Bull. Soc. chim.*, 1942, **9**, 111, 841). It was of interest to examine the odour of its isologues. 2-*tert.*-Butyl-4 : 5 : 6 : 7-tetrahydro-4-oxothionaphthen (I), prepared from 2-*tert.*-butylthiophen by the succinic anhydride method (cf. Buu-Hoï, Hoán, and Khôi, *J. Org. Chem.*, 1950, **15**, 957), did in fact, in the vapour state, have the characteristic burning-sandalwood smell. The 3-*tert.*-butyl isomer, prepared from 3-*tert.*-butylthiophen, had a less marked and less pleasant odour. A chemical difference was that the former readily underwent a Pfitzinger reaction with isatin to give 5′-*tert.*-butyl-3 : 4-dihydrothiopheno(3′ : 2′-1 : 2)acridine-5-carboxylic acid (III), whereas the latter gave a negligible yield, probably on account of steric hindrance by the *tert.*-butyl group.



(I) (II) (III) (IV)

The successful synthesis of the thionaphthen (II) showed that succinoylation of 3-*tert.*-butylthiophen, which yielded only one reaction product, occurred at position 5, in contrast with the acylation of 3-methylthiophen which takes place mostly at position 2 (Hartough and Kosak, *J. Amer. Chem. Soc.*, 1947, **69**, 3093), a discrepancy probably due to the steric effect of the *tert.*-butyl radical. Formylation of 3-*tert.*-butylthiophen readily gave a single aldehyde, which was therefore taken to be 4-*tert.*-butyl-2-thenaldehyde; likewise, acetylation gave a single ketone, considered on the same grounds to be 2-acetyl-4-*tert.*-butylthiophen. This ketone underwent a Pfitzinger reaction with isatin to give 2-(4-*tert.*-butyl-2-thienyl)cinchoninic acid, and oxidation with sodium hypobromite to give 4-*tert.*-butyl-2-thenoic acid.

Formylation of 2 : 5-di-*tert.*-butylthiophen gave a good yield of 2 : 5-di-*tert.*-butyl-3-thenaldehyde; condensation with benzyl cyanide gave the acrylonitrile (IV; R = H). 2 : 5-Di-*tert.*-butyl-3-methylthiophen, prepared from the aldehyde by Wolff–Kishner reduction, also gave the aldehyde, and thence the acrylonitrile (IV; R = Me) and 2 : 5-di-*tert.*-butyl-3 : 4-dimethylthiophen. 3-Acetyl-2 : 5-di-*tert.*-butylthiophen, unlike the aldehydes, gave no ketonic derivatives or cinchoninic acid, nor could it be oxidised by sodium hypobromite.

5-*iso*Propyl-2-thenaldehyde was prepared; its odour was like that of *p*-*iso*propylbenzaldehyde. Both 2-2′-thienylideneheptanol, prepared by condensing 2-thenaldehyde with heptanal, and α-*n*-pentylcinnamaldehyde (Rutowski and Korolew, *J. prakt. Chem.*,

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1928, **119**, 273) had a jasmin-like scent; similarly, a series of esters prepared from 2-thenoic acid had odours resembling those of their benzene isologues.

There is thus an analogy between the benzene and thiophen derivatives in respect of odour; but no attempt was made in the present work at a precise assessment on a physiological basis.

Experimental

β-(5-tert.-*Butyl-2-thenoyl)propionic Acid.*—To an ice-cooled, stirred solution of 2-*tert.*-butylthiophen (22 g.) and succinic anhydride (20 g.) in nitrobenzene (120 c.c.), finely powdered aluminium chloride (50 g.) was added portionwise. The mixture was kept for 16 hr. at room temperature, then decomposed with ice, and the nitrobenzene steam-distilled. The *keto-acid* was taken up in aqueous sodium carbonate and recrystallised from benzene, giving colourless prisms (31 g.), m. p. 114° (Found: C, 59·7; H, 6·8. $C_{12}H_{16}O_3S$ requires C, 60·0; H, 6·7%).

γ-(5-tert.-*Butyl-2-thienyl)butyric Acid.*—The foregoing acid (28 g.) was heated with 85% hydrazine hydrate (30 g.) and potassium hydroxide (25 g.) in diethylene glycol (100 c.c.) to 190—200° with removal of water, and the mixture then refluxed for 2 hr., diluted with water, and acidified with dilute hydrochloric acid. The reduction *product*, taken up in benzene, was purified by vacuum-distillation, and formed colourless leaflets (20 g.), m. p. 47°, b.p. 214°/24 mm., from ligroin (Found: C, 63·5; H, 8·2. $C_{12}H_{18}O_2S$ requires C, 63·7; H, 8·0%).

2-tert.-*Butyl*-4 : 5 : 6 : 7-*tetrahydro*-4-*oxothionaphthen* (I).—The butyric acid (10 g.) was converted into the acid chloride by thionyl chloride (20 g.) and a few drops of pyridine, treated in cold carbon disulphide (50 c.c.) with stannic chloride (25 g., dissolved in 20 c.c. of carbon disulphide), refluxed for 2 hr., and worked up in the usual way. The *ketone* (4 g.) formed a pale yellow oil, b. p. 170—171°/13 mm., n_D^{25} 1·5699 (Found: C, 68·9; H, 7·8. $C_{12}H_{16}OS$ requires C, 69·2; H, 7·7%). The *semicarbazone* formed needles, m. p. 249°, from ethanol (Found: N, 15·6. $C_{13}H_{19}ON_3S$ requires N, 15·8%).

5′-tert.-*Butyl*-3 : 4-*dihydrothiopheno*(3′ : 2′-1 : 2)*acridine*-5-*carboxylic Acid* (III).—A solution of the foregoing ketone (2·1 g.), isatin (1·5 g.), and potassium hydroxide (1·7 g.) in ethanol (15 c.c.) was gently refluxed for 12 hr. After dilution with water and ether-extraction of neutral impurities, acidification with acetic acid gave a precipitate (2 g.) which crystallised as pale yellow prisms, m. p. 231°, from ethanol (Found: C, 71·0; H, 5·6. $C_{20}H_{19}O_2NS$ requires C, 71·2; H, 5·6%).

4-tert.-*Butyl-2-thenaldehyde.*—A mixture of 3-*tert.*-butylthiophen (17·5 g.), *N*-methylformanilide (22·5 g.), and phosphorus oxychloride (24 g.) was refluxed for 2 hr., then poured into aqueous sodium acetate, and the mixture was steam-distilled. The *aldehyde* was taken up in ether, washed with dilute hydrochloric acid, then with water, dried (Na_2SO_4), and purified by distillation, to form a pale yellow oil (18 g.), b. p. 249—250°, n_D^{22} 1·5320 (Found: C, 64·2; H, 7·2. $C_9H_{12}OS$ requires C, 64·3; H, 7·1%). It gave a *semicarbazone*, leaflets, m. p. 221°, from ethanol (Found: N, 18·4. $C_{10}H_{15}ON_3S$ requires N, 18·7%), *thiosemicarbazone*, colourless prisms, m. p. 186°, from ethanol (Found: C, 49·5; H, 6·2. $C_{10}H_{15}N_3S_2$ requires C, 49·8; H, 6·2%), 4-*oxo*-Δ^2-*thiazolin*-2-*ylhydrazone*, colourless prisms, m. p. 315°, from ethanol (Found: C, 51·0; H, 5·2. $C_{13}H_{15}ON_3S_2$ requires C, 51·2; H, 5·3%), 2 : 4-*dinitrophenylhydrazone*, red needles, m. p. 221°, from acetic acid (Found: N, 16·2. $C_{15}H_{16}O_4N_4S$ requires N, 16·1%), and *oxime*, colourless needles, m. p. 79°, from methanol (Found: C, 58·8; H, 7·4. $C_9H_{15}ONS$ requires C, 59·0; H, 7·1%).

4-tert.-*Butyl*-2-*methylthiophen.*—Obtained by reduction of the foregoing aldehyde (8·5 g.) by means of hydrazine hydrate (14 g.) and potassium hydroxide (14 g.) in diethylene glycol (60 c.c.), this *compound* formed a pale yellow oil (7 g.), b. p. 195°, n_D^{24} 1·5025 (Found: C, 70·0; H, 9·2. $C_9H_{14}S$ reuires C, 70·1; H, 9·1%).

2-*Acetyl*-4-tert.-*butylthiophen.*—To an ice-cooled solution of 3-*tert.*-butylthiophen (14 g.) and acetyl chloride (8 g.) in carbon disulphide (200 c.c.), stannic chloride (30 g.) was added portionwise. The mixture was kept at room temperature for 1 hr., poured on ice, then worked up in the usual way. The *ketone* (15 g.) was a pale yellow oil, b. p. 259°, n_D^{23} 1·5322 (Found C, 65·8; H, 7·7. $C_{10}H_{14}OS$ requires C, 65·9; H, 7·7%). It gave a 2 : 4-*dinitrophenylhydrazone*, red needles, m. p. 226°, from acetic acid (Found: N, 15·8. $C_{16}H_{16}O_4N_4S$ requires N, 15·5%), *oxime*, colourless needles, m. p. 113°, from ethanol (Found: C, 60·6; H, 7·5. $C_{10}H_{15}ONS$ requires C, 60·9; H, 7·6%), semicarbazone, m. p. 249°, thiosemicarbazone, m. p. 192°, and 4-oxo-Δ^2-thiazolin-2-ylhydrazone, m. p. 305°. 2-(4-tert.-*Butyl*-2-*thienyl*)*cinchoninic acid*, prepared in 90% yield by means of isatin, formed pale yellow prisms, m. p. 172°, from ethanol (Found: C, 69·1; H, 5·3. $C_{18}H_{17}O_2NS$ requires C, 69·5; H, 5·5%).

4-tert.-*Butyl*-2-*thenoic Acid*.—2-Acetyl-4-*tert*.-butylthiophen (19 g.) was oxidised with aqueous sodium hypobromite (from 16 g. of sodium hydroxide and 8·2 c.c. of bromine); the *acid* obtained (60% yield) formed prisms, m. p. 77°, from water (Found: C, 58·5; H, 6·6. $C_9H_{12}O_2S$ requires C, 58·7; H, 6·5%).

β-(4-tert.-*Butyl*-2-*thenoyl*)*propionic Acid*.—Prepared from 3-*tert*.-butylthiophen as for the 2-isomer and in similar yield, this *acid* formed colourless prisms, m. p. 119°, from benzene (Found: C, 59·7; H, 6·5%). γ-(3-tert.-*Butyl*-5-*thienyl*)*butyric acid* formed a pale yellow, viscous oil, b. p. 200—201°/13 mm. (Found: C, 63·5; H, 8·3%).

3-tert.-*Butyl*-4 : 5 : 6 : 7-*tetrahydro*-4-*oxothiophen*.—This *ketone* formed a pale yellow oil, b. p. 179°/13 mm., n_D^{25} 1·5669, whose vapours had a less pleasant odour than the isomeric ketone (Found: C, 69·0; H, 8·0%); it gave no cinchoninic acid with isatin. The *semicarbazone* formed needles, m. p. 238° (Found: C, 58·6; H, 7·3%).

2 : 5-*Di*-tert.-*butyl*-3-*thenaldehyde*.—A mixture of 2 : 5-di-*tert*.-butylthiophen (25 g.), phosphorus oxychloride (25 g.), and *N*-methylformanilide (24 g.) was heated for 3 hr. on the water-bath and worked up in the usual way; the *aldehyde* formed a pale yellow oil, b. p. 137°/13 mm., n_D^{21} 1·5147 (Found: C, 69·5; H, 9·0. $C_{13}H_{20}OS$ requires C, 69·6; H, 8·9%), and gave a *semicarbazone*, prisms, m. p. 231° (Found: N, 14·6. $C_{14}H_{23}ON_3S$ requires N, 14·9%), *oxime*, prisms, m. p. 106°, from ethanol (Found: C, 65·0; H, 9·0. $C_{13}H_{21}ONS$ requires C, 65·3; H, 8·8%), and 2 : 4-*dinitrophenylhydrazone*, red needles, m. p. 219°, from acetic acid (Found: N, 14·2. $C_{19}H_{24}O_4N_4S$ requires N, 13·9%).

1-*Phenyl*-2-(2 : 5-*di*-tert.-*butyl*-3-*thienyl*)*acrylonitrile* (IV; R = H).—This *compound* crystallised as pale yellow needles, m. p. 136°, from ethanol, giving a deep orange solution with sulphuric acid (Found: C, 78·2; H, 7·6. $C_{21}H_{25}NS$ requires C, 78·0; H, 7·7%).

2 : 5-*Di*-tert.-*butyl*-3-*methylthiophen*.—Prepared from 2 : 5-di-*tert*.-butyl-3-thenaldehyde (10 g.), hydrazine hydrate (15 g.), and potassium hydroxide (15 g.) in diethylene glycol (50 c.c.), this *compound* formed a pale yellow oil (8 g.), b. p. 119°/13 mm., n_D^{23} 1·4952 (Found: C, 74·2; H, 10·5. $C_{13}H_{22}S$ requires C, 74·3; H, 10·5%).

2 : 5-*Di*-tert.-*butyl*-4-*methyl*-3-*thenaldehyde*.—Prepared from the foregoing compound (8 g.), phosphorus oxychloride (8 g.), and *N*-methylformanilide (7 g.), the *aldehyde* (7 g.) was a pale yellow, viscous oil, b. p. 155°/13 mm., n_D^{21} 1·5091 (Found: C, 70·4; H, 9·5. $C_{14}H_{22}OS$ requires C, 70·6; H, 9·2%); it gave a *semicarbazone*, needles, m. p. 225°, from ethanol (Found: N, 13·9. $C_{15}H_{25}ON_3S$ requires N, 14·2%), *oxime*, prisms, m. p. 95°, from ethanol (Found: C, 66·3; H, 9·3. $C_{14}H_{23}ONS$ requires C, 66·4; H, 9·1%), and orange-red 2 : 4-dinitrophenylhydrazone, m. p. 221°.

2-(2 : 5-*Di*-tert.-*butyl*-4-*methyl*-3-*thienyl*)-1-*phenylacrylonitrile* (IV; R = Me).—This *compound* crystallised as yellow needles, m. p. 144° from ethanol, giving an orange-red solution with sulphuric acid (Found: C, 78·0; H, 8·3. $C_{22}H_{27}NS$ requires C, 78·3; H, 8·0%).

2 : 5-*Di*-tert.-*butyl*-3 : 4-*dimethylthiophen*.—Obtained in only 60% yield, this *compound* was a pale yellow oil, b. p. 139°/13 mm., n_D^{19} 1·4832 (Found: C, 74·9; H, 10·9. $C_{14}H_{24}S$ requires C, 75·0; H, 10·7%).

5-iso*Propyl*-2-*thenaldehyde*.—Prepared in the usual way from 2-*iso*propylthiophen (Schleicher, *Ber.*, 1886, **19**, 67?) (b. p. 154°, n_D^{20} 1·5630), the *aldehyde* (78% yield) was a pale yellow oil, b. p. 239°, n_D^{19} 1·5604, with a strong cumin odour resembling that of *p*-*iso*propylbenzaldehyde (Found: C, 62·3; H, 6·5. $C_8H_{10}OS$ requires C, 62·3; H, 6·5%). The *semicarbazone* formed needles, m. p. 219°, from ethanol (Found: C, 51·0; H, 6·3. $C_9H_{13}ON_3S$ requires C, 51·2; H, 6·2%), the *thiosemicarbazone* yellowish prisms, m. p. 203°, from ethanol (Found: C, 47·3; H, 5·5. $C_9H_{13}N_3S_2$ requires C, 47·6; H, 5·7%); and the 4-*oxo*-Δ^2-*thiazolin*-2-*ylhydrazone* colourless needles, m. p. 257° (decomp.) (Found: C, 49·1; H, 5·0. $C_{11}H_{13}ON_3S_2$ requires C, 49·4; H, 4·9%). 1-*Phenyl*-2-(5-iso*propyl*-2-*thienyl*)*acrylonitrile*, obtained by use of benzyl cyanide, formed yellowish needles, m. p. 72°, from ethanol, giving an orange colour with sulphuric acid (Found: C, 75·8; H, 6·2. $C_{16}H_{15}NS$ requires C, 75·9; H, 5·9%).

2-2′-*Thienylideneheptanal*.—To a solution of 2-thenaldehyde (11·2 g.) and heptanal (11·4 g.) in ethanol (100 c.c.) and water (500 c.c.), 10% aqueous sodium hydroxide (25 c.c.) was added, and the mixture was kept at room temperature for 2 days, with frequent shaking. After acidification with acetic acid, the *product* was taken up in ether and vacuum-fractionated, giving a colourless oil (15 g.), b. p. 192—194°/35 mm., n_D^{25} 1·5686 (Found: C, 69·0; H, 7·8. $C_{12}H_{16}OS$ requires C, 69·2; H, 7·7%). The *semicarbazone* formed colourless prisms, m. p. 132—133°, from ethanol (Found: C, 58·6; H, 7·4. $C_{13}H_{19}ON_3S$ requires C, 58·9; H, 7·2%).

Esters of 2-*Thenoic and* 5-tert.-*Butyl*-2-*thenoic Acid*.—These *esters* were prepared by the

reaction of 2-thenoyl chloride or 5-*tert.*-butyl-2-thenoyl chloride on the appropriate alcohol in ether or benzene; they are listed in the Table.

Alkyl	B. p./mm.	n_D (temp.)	Formula	Found (%) C	Found (%) H	Reqd. (%) C	Reqd. (%) H
Esters of 2-thenoic acid.							
Pr^n	124—125°/24	1·5137 (28°)	$C_9H_{10}O_2S$	56·3	6·1	56·5	5·9
Pr^i	110°/22	1·5128 (26)	$C_9H_{10}O_2S$	56·2	6·0	56·5	5·9
Bu^n	137—138°/24	1·5112 (27)	$C_9H_{12}O_2S$	58·8	6·6	58·7	6·5
Bu^t	129°/22	1·5088 (27)	$C_9H_{12}O_2S$	58·4	6·7	58·7	6·5
n-Pentyl	152—153°/27	1·5079 (27)	$C_{10}H_{14}O_2S$	60·5	7·3	60·6	7·1
*iso*Pentyl	142—143°/22	1·5049 (28)	$C_{10}H_{14}O_2S$	60·8	7·0	60·6	7·1
n-Decyl	207—208°/20	1·4943 (26)	$C_{15}H_{24}O_2S$	67·0	8·8	67·2	9·0
Tetrahydrogeranyl	198°/22	1·4986 (27)	$C_{15}H_{24}O_2S$	67·3	9·2	67·2	9·0
n-Dodecyl	224—225°/20	1·4901 (28)	$C_{17}H_{28}O_2S$	68·6	9·4	68·9	9·5
n-Tetradecyl	245—246°/20	1·4891 (27)	$C_{19}H_{32}O_2S$	70·3	10·2	70·4	9·9
n-Hexadecyl	266—268°/22	1·4882 (26)	$C_{21}H_{36}O_2S$	71·3	10·2	71·6	10·2
Citronellyl	198—199°/20	1·4981 (26)	$C_{15}H_{22}O_2S$	67·5	8·5	67·7	8·3
Benzyl	195—196°/24	1·5786 (25)	$C_{12}H_{10}O_2S$	66·0	4·7	66·1	4·6
2-Phenylethyl	199—201°/18	1·5731 (26)	$C_{13}H_{12}O_2S$	67·0	5·5	67·2	5·2
3-Phenylpropyl	222°/24	1·5649 (26)	$C_{14}H_{14}O_2S$	68·2	5·8	68·3	5·7
Esters of 5-tert.-butyl-2-thenoic acid.							
Et	150—151°/20	1·5138 (26)	$C_{11}H_{16}O_2S$	62·0	7·3	62·3	7·5
*iso*Pentyl	174—175°/20	1·5025 (25)	$C_{14}H_{22}O_2S$	66·0	8·8	66·1	8·7
Benzyl	226—227°/29	1·5608 (27)	$C_{16}H_{18}O_2S$	70·3	6·6	70·1	6·6
2-Phenylethyl	238—239°/31	1·5493 (27)	$C_{17}H_{20}O_2S$	70·5	7·2	70·8	6·9

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Additive Compounds as Possible Intermediates in Substitution Processes. Part I.

By F. BELL and J. A. GIBSON.

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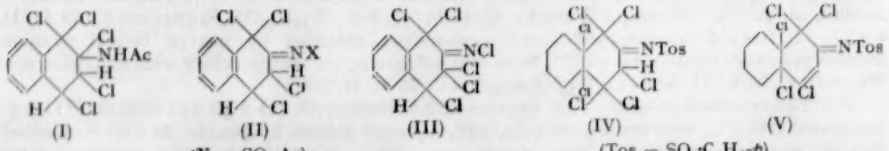
The chlorination of a number of aromatic bases and their derivatives has been examined to see whether additive compounds could be isolated. Positive results were obtained only with 5 : 6 : 7 : 8-tetrahydro-*N*-toluene-*p*-sulphonyl-2-naphthylamine.

CLAUS and PHILIPSON (*J. pr. Chem.*, 1891, **43**, 58) by chlorination of *N*-acetyl-2-naphthylamine obtained the compound (I), and Bell (*J.*, 1953, 3035) by chlorination of various sulphonyl derivatives of β-naphthylamine obtained compounds of type (II). Durand and Huguenin A.G. (D.R.-P. 400,254) have described conditions under which many bases react with chlorine to give compounds of type (III). As a working hypothesis it is accepted that the intermediate formation of such compounds may be responsible for substitution products of abnormal orientation. Conversely, the isolation of an abnormal substitution product would encourage a search for intermediate additive compounds. Thus, the



(I) (II) (X = SO_2·Ar) (III) (IV) (V) (Tos = SO_2·C_7H_7-*p*)

production of the 4-bromo-derivative from *N*-acetyl-5 : 6 : 7 : 8-tetrahydro-2-naphthylamine (Smith, *J.*, 1904, **85**, 728) suggests that in this reaction an addition–elimination mechanism may be involved. This is of particular interest because, whereas in the examples given above the addition has resulted in the conversion of a naphthalene derivative into a tetralin with one true aromatic nucleus, here addition involves the partial or complete

saturation of a benzene nucleus. The present investigation sought to ascertain whether additive compounds could be obtained from appropriate derivatives of tetralin, diphenyl, and fluorene on treatment with halogens.

First, it was found that *N*-acetyl-5 : 6 : 7 : 8-tetrahydro-1-naphthylamine on chlorination gave a monochloro-derivative and then the hydrochloride of a dichloro-derivative, whilst *N*-acetyl-5 : 6 : 7 : 8-tetrahydro-2-naphthylamine, under the same conditions, yielded uncrystallisable oils. Next, 5 : 6 : 7 : 8-tetrahydro-*N*-toluene-*p*-sulphonyl-1-naphthylamine gave on chlorination a dichloro-derivative and on bromination a mixture of the 4-bromo-derivative with a dibromo-derivative. In all these reactions no evidence was obtained for the formation of additive compounds.

On the other hand, 5 : 6 : 7 : 8-tetrahydro-*N*-toluene-*p*-sulphonyl-2-naphthylamine in chloroform with chlorine gave a mixture of two closely related compounds, probably (IV) and (V), together with toluene-*p*-sulphonamide. Compound (V) is readily produced from (IV) by dissolution in aniline, and either of these might by decomposition yield toluene-*p*-sulphonamide and a derivative of β-tetralone (or simpler breakdown products). Analogous additive compounds were not obtained on bromination; only substitution products were obtained, the nature depending on the solvent employed.

Chlorination of 2-aminodiphenyl under the conditions outlined in D.R.-P. 400,254 led only to 2-amino-3 : 5-dichlorodiphenyl in *ca.* 10% yield. 4-Aminodiphenyl and 2-aminofluorene, treated similarly, gave plastic masses. Chlorination of 2-toluene-*p*-sulphonamidodiphenyl under a variety of conditions led only to the 5-chloro-derivative. 4-Toluene-*p*-sulphonamidodiphenyl gave first the 3-chloro- and then the 3 : 4′-dichloro-derivative. 2-Toluene-*p*-sulphonamidofluorene and 2-acetamidofluorene gave dichloro-derivatives. No addition compounds were isolated in this series of experiments.

Experimental

Chlorination of 2-aminodiphenyl (25 g.) by the general method of D.R.-P. 400,254 led to the hydrochloride of the 3 : 5-dichloro-base (3·5 g.) and a dark, undistillable viscous mass. 3 : 5-Dichloro-2-aminodiphenyl could be recovered from hot acetic anhydride alone, but in the presence of a drop of sulphuric acid it gave the 2-*acetamido*-compound, which formed prisms, m. p. 162°, from ethanol (Found : Cl, 25·3. $C_{14}H_{11}ONCl_2$ requires Cl, 25·3%). With toluene-*p*-sulphonyl chloride in pyridine the dichloro-base reacted slowly and it was better to use slightly more than 2 mols. of the chloride and leave the mixture overnight. The product was freed from any ditoluene-*p*-sulphonamide by solution in warm piperidine and then crystallised from ethanol to give 3 : 5-*dichloro*-2-*toluene*-p-*sulphonamidodiphenyl* as needles, m. p. 159° (Found : Cl, 17·9. $C_{19}H_{15}O_2NCl_2S$ requires Cl, 18·1%).

Chlorination of 2-*Toluene*-p-*sulphonamidodiphenyl.*—Passage of chlorine (3 mols.) into a chloroform solution of the sulphonamide, or addition of sulphuryl chloride (1—3 mols.) to a similar solution, or treatment of the sulphonamide with excess of sulphuryl chloride all led to 5-*chloro*-2-*toluene*-p-*sulphonamidodiphenyl*, which crystallised from ethanol or benzene–light petroleum (b. p. 60—80°) in prisms, m. p. 110° (Found : Cl, 10·4. $C_{19}H_{16}O_2NClS$ requires Cl, 9·9%). This compound was unchanged after several hours in cold sulphuric acid. The structure was confirmed by its preparation from 2-amino-5-chlorodiphenyl (Scarborough and Waters, *J.*, 1927, 90).

Chlorination of 4-*Toluene*-p-*sulphonamidodiphenyl.*—(*a*) The sulphonamide was warmed until dissolved with excess of sulphuryl chloride, and the excess was then evaporated off. The residual light brown treacle was very soluble in acetic acid and in ethanol, but the solution in benzene slowly deposited prisms of 3 : 4′-*dichloro*-4-*toluene*-p-*sulphonamidodiphenyl*, m. p. 133° after recrystallisation from acetic acid (Found : Cl, 17·5. $C_{19}H_{15}O_2NCl_2S$ requires Cl, 18·1%). By dissolution in cold sulphuric acid this compound gave 4-*amino*-3 : 4′-*dichlorodiphenyl*, which crystallised from aqueous ethanol in plates, m. p. 100° (Found : C, 60·6; H, 3·5. $C_{12}H_9NCl_2$ requires C, 60·5; H, 3·8%), and gave an acetyl derivative, m. p. 184° (Kenyon and Robinson, *J.*, 1926, 3053, give m. p. 184°). (*b*) Chlorine (1 mol.) was passed into a solution of the sulphonamide in chloroform, the solution concentrated, and light petroleum added. The first crop consisted of essentially unchanged material but the second crop was 3-*chloro*-4-*toluene*-p-*sulphonamidodiphenyl*, which formed large prisms, m. p. 107°, from ethanol (Found : Cl, 9·7. $C_{19}H_{16}O_2NClS$ requires Cl, 9·8%). This compound was unchanged after 2 hr. in sulphuric acid.

It was alternatively prepared from 4-amino-3-chlorodiphenyl (Scarborough and Waters, *J.*, 1926, 557). By interaction with sulphuryl chloride it gave the above described 3 : 4'-dichloro-compound, alternatively prepared from *4'-chloro-4-toluene*-p-*sulphonamidodiphenyl* (Found: C, 63·2; H, 4·6. $C_{19}H_{16}O_2NClS$ requires C, 63·8; H, 4·5%). The latter, obtained from 4-amino-4'-chlorodiphenyl, crystallised from ethanol in needles, m. p. 156°.

Chlorination of 2-Toluene-p-*sulphonamidofluorene.*—(*a*) On addition of the sulphonamide (Bell and Mulholland, *J.*, 1949, 2021) to sulphuryl chloride a brisk reaction set in with development of a violet colour. When reaction had ceased the excess of sulphuryl chloride was evaporated off, and the residue crystallised from chloroform or acetic acid to give 3(?) : *7-dichloro-2-toluene*-p-*sulphonamidofluorene* as a cotton-wool-like mass of needles, m. p. 215° (Found: Cl, 17·7. $C_{20}H_{15}O_2NCl_2S$ requires Cl, 17·6%). On dissolution in cold sulphuric acid this gave *2-amino*-3(?) : *7-dichlorofluorene*, which formed needles, m. p. 161°, from aqueous ethanol (Found: C, 61·6; H, 3·7. $C_{13}H_9NCl_2$ requires C, 62·4; H, 3·6%). The *acetyl* derivative (by use of acetic anhydride) crystallised from acetic acid in needles, m. p. 261° (Found: Cl, 24·0. $C_{15}H_{12}ONCl$ requires Cl, 24·3%). (*b*) Chlorine (1 mol.) was passed into a solution of the sulphonamide in chloroform, and the solution concentrated and allowed to cool. The crystalline crop after recrystallisation from acetic acid gave 3(?)-*chloro-2-toluene*-p-*sulphonamidofluorene* in prisms, m. p. 151° (Found: Cl, 9·5. $C_{20}H_{16}O_2NClS$ requires Cl, 9·6%). It was converted into the above dichloro-compound by solution in sulphuryl chloride.

7-Chloro-2-toluene-p-*sulphonamidofluorene*, obtained from 2-amino-7-chlorofluorene (Gutmann and Francis, *J. Amer. Chem. Soc.*, 1951, **73**, 4033), crystallised from acetic acid in needles, m. p. 202° (Found: Cl, 10·4. $C_{20}H_{16}O_2NClS$ requires Cl, 9·6%). It gave the above dichloro-compound with sulphuryl chloride.

Chlorination of 2-Acetamidofluorene.—Chlorine (1 mol.) was passed into a solution of the compound in acetic acid (10 parts). The resulting precipitate was filtered off, warmed with aqueous ammonia, and dried. Extraction with hot chloroform left pure 2-acetamido-3(?) : 7-dichlorofluorene (above) and the filtrate on concentration gave a crude monochloro-derivative, m. p. 200° (Found: C, 67·9; H, 4·6. Calc. for $C_{15}H_{12}ONCl$: C, 69·9; H, 4·7%). A similar result was obtained by using chloroform as solvent.

5 : 6 : 7 : 8-*Tetrahydro*-N-*toluene*-p-*sulphonyl*-1-*naphthylamine*, from the base and toluene-*p*-sulphonyl chloride, crystallised from ethanol in prisms, m. p. 123° (Found: C, 68·1; H, 6·4. $C_{17}H_{19}O_2NS$ requires C, 67·8; H, 6·3%). Chlorine (3 mols.) was passed into a solution of this sulphonamide in cold chloroform, and the chloroform evaporated. The residue solidified when rubbed with acetic acid and was then purified by repeated recrystallisation from acetic acid to yield *dichloro-5* : 6 : 7 : 8-*tetrahydro*-N-*toluene*-p-*sulphonyl*-1-*naphthylamine* as needles, m. p. 170° (Found: Cl, 18·7. $C_{17}H_{17}O_2NCl_2S$ requires Cl, 19·2%), hydrolysed in cold sulphuric acid to yield an oily base, which gave an acetyl derivative, m. p. 200° (below).

Bromination of 5 : 6 : 7 : 8-Tetrahydro-N-*toluene*-p-*sulphonyl*-1-*naphthylamine.*—Bromine (2 mols.) in chloroform was added to the sulphonamide in chloroform, and the mixture boiled to expel hydrogen bromide. On cooling there separated needles, m. p. 244°, of the hydrobromide of the dibromo-base, which with excess of aqueous ammonia gave a liquid base, converted by acetic anhydride into an acetyl derivative, which formed needles, m. p. 198—200°, from ethanol (Morgan, Micklethwait, and Winfield, *J.*, 1904, **85**, 736, give m. p. 198—199°). After evaporation of the chloroform there remained a viscous oil which yielded crystalline material, m. p. *ca.* 124°, after solution in hot ethanol. This material, after removal of impurities by solution in cold sulphuric acid and reprecipitation by water, gave *4-bromo-5* : 6 : 7 : 8-*tetrahydro*-N-*toluene*-p-*sulphonyl*-1-*naphthylamine* as prisms, m. p. 140°, after recrystallisation from acetic acid (Found: Br, 21·6. $C_{17}H_{18}O_2NBrS$ requires Br, 21·0%). It was alternatively prepared from 4-bromo-5 : 6 : 7 : 8-tetrahydro-1-naphthylamine (*idem*, *loc. cit.*).

Chlorination of 5 : 6 : 7 : 8-Tetrahydro-N-*toluene*-p-*sulphonyl*-2-*naphthylamine.*—Chlorine (3 mols.) was passed into a solution of the sulphonamide (Buu-Hoï and Jacquignon, *J.*, 1951, 2966) in chloroform, and the solution diluted with light petroleum. The first crop consisted of toluene-*p*-sulphonamide. The second, after crystallisation from acetic acid in which it was sparingly soluble, formed needles, m. p. 163° (decomp.). The third was a sticky mass, which solidified completely when rubbed with acetic acid and, after recrystallisation from acetic acid, formed needles, m. p. 183° (decomp.). The compound, m. p. 163°, was unchanged after dissolution in pyridine but reacted briskly with aniline to give a highly coloured product from which only the compound, m. p. 183°, could be isolated in a pure condition. When compound, m. p. 163°, was kept at 170° until gas evolution ceased the residue was a dark, uncrystallisable oil. It is suggested that the compound, m. p. 163°, is 1 : 1 : 3 : 4 : 9 : 10-*hexachloro-2-toluene*-

p-*sulphonamidodecalin* (IV) (Found: Cl, 40·7. $C_{17}H_{17}O_2NCl_6S$ requires Cl, 41·6%) and the compound, m. p. 183°, formed from this by loss of hydrogen chloride, is 1 : 1 : 4 : 9 : 10-*pentachloro*-2-*toluene*-p-*sulphonimido*-Δ^3-*octalin* (V) (Found: Cl, 37·3. $C_{17}H_{16}O_2NCl_5S$ requires Cl, 37·3%).

The same two compounds were obtained by chlorination of the sulphonamide in acetic acid solution; chlorination by dissolution in sulphuryl chloride gave the compound, m. p. 163°, in very small yield together with an uncrystallisable oil.

Bromination of 5 : 6 : 7 : 8-*Tetrahydro*-N-*toluene*-p-*sulphonyl*-2-*naphthylamine*.—(*a*) Bromine (1 mol.) in chloroform was added to the compound dissolved in chloroform. After the brisk reaction the solution was warmed to expel hydrogen bromide and then filtered from a deposit of the hydrobromide of 1-bromo-5 : 6 : 7 : 8-tetrahydro-2-naphthylamine (acetyl derivative, m. p. 126°; Sandin and Evans, *J. Amer. Chem. Soc.*, 1939, **61**, 2916, give m. p. 126—127°). On removal of the chloroform there remained a thick oil which after solution in either ethanol or acetic acid gave material, m. p. 100—115°, which could not be purified. It was redissolved in chloroform and treated with bromine (1 mol.). This led to the deposition of the hydrobromide of 1 : 3-dibromo-5 : 6 : 7 : 8-tetrahydro-2-naphthylamine (below). On evaporation of the chloroform there remained a viscous oil from which crystalline material was not obtained. (*b*) Bromine (2 mols.) was added to the sulphonamide dissolved in cold pyridine, and after 2 hr. the mixture was decomposed with dilute hydrochloric acid. The resultant solid on crystallisation from acetic acid gave 1 : 3-*dibromo*-5 : 6 : 7 : 8-*tetrahydro*-N-*toluene*-p-*sulphonyl*-2-*naphthylamine* as needles, m. p. 195°, in almost theoretical yield (Found: Br, 34·9. $C_{17}H_{17}O_2NBr_2S$ requires Br, 34·8%). By solution in cold sulphuric acid it gave 1 : 3-*dibromo*-5 : 6 : 7 : 8-*tetrahydro*-2-*naphthylamine*, which crystallised from methanol in needles, m. p. 65° (Found: C, 38·8; H, 3·4. $C_{10}H_{11}NBr_2$ requires C, 39·4; H, 3·6%). The position of the bromine atoms is assigned by analogy with the results obtained from the bromination of other sulphonamides in pyridine (see, *e.g.*, Bell, *J.*, 1931, 2340; 1932, 2732; Consden and Kenyon, *J.*, 1935, 1593; Hodgson and Dean, *J.*, 1950, 821) and also the known 1 : 3-dibromination of 5 : 6 : 7 : 8-tetrahydro-2-naphthol and the 1 : 3-dinitration of 5 : 6 : 7 : 8-tetrahydro-2-acetonaphthalide (Schroeter, *Annalen*, 1922, **426**, 39).

1- and 4-Bromo-5 : 6 : 7 : 8-tetrahydro-2-naphthylamines were prepared by Smith's method (*loc. cit.*) and yielded, respectively, 1-*bromo*-, prisms, m. p. 127°, from ethanol (Found: C, 53·2; H, 4·5. $C_{17}H_{18}O_2NBrS$ requires C, 53·7; H, 4·7%), and 4-*bromo*-5 : 6 : 7 : 8-*tetrahydro*-N-*toluene*-p-*sulphonyl*-2-*naphthylamine*, prisms, m. p. 133°, from ethanol (Found: C, 53·7; H, 4·9%). A mixture of the isomerides had m. p. <120°.

Chlorination of N-*Acetyl*-5 : 6 : 7 : 8-*Tetrahydro*-1-*naphthylamine*.—Chlorine (1 mol.) was passed into a chloroform solution of the compound and most of the chloroform removed. The crystalline crop after recrystallisation from ethanol gave N-*acetyl* 4(?)-*chloro*-5 : 6 : 7 : 8-*tetrahydro*-1-*naphthylamine* in white needles, m. p. 184° (Found: Cl, 16·1. $C_{12}H_{14}ONCl$ requires Cl, 15·9%); yield, 2·9 g. from 5 g. This chloro-derivative in chloroform was treated with excess of chlorine. On cooling, there separated needles, m. p. 188° (decomp.) of the *hydrochloride* of *N*-acetyl-2 : 4(?)-dichloro-5 : 6 : 7 : 8-tetrahydro-1-naphthylamine (Found: Cl, 35·8. $C_{12}H_{13}ONCl_2,HCl$ requires Cl, 36·2%). When heated above its m. p. or dissolved in pyridine, this gave N-*acetyl*-2 : 4(?)-*dichloro*-5 : 6 : 7 : 8-*tetrahydro*-1-*naphthylamine*, which crystallised from acetic acid in needles, m. p. 199—200° (Found: C, 54·9; H, 4·9. $C_{12}H_{13}ONCl_2$ requires C, 55·8; H, 5·0%).

The introduction of chlorine (1 mol.) into *N*-acetyl-5 : 6 : 7 : 8-tetrahydro-2-naphthylamine in chloroform led only to a viscous mass.

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HERIOT-WATT COLLEGE, EDINBURGH. [*Received, August 25th*, 1954.]

mero*Cyanines Derived from Thio-oxindole. Part III.* Trinuclear* mero*Cyanines.*

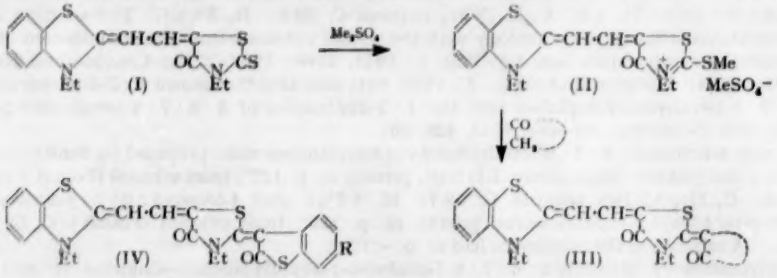
[Reprint Order No. 5696.]

By R. H. Glauert, Frederick G. Mann, and A. J. Wilkinson.

Four trinuclear *mero*cyanines containing the thio-oxindole nucleus have been prepared. The dyes are compared briefly with their isomers derived from thioindoxyl.

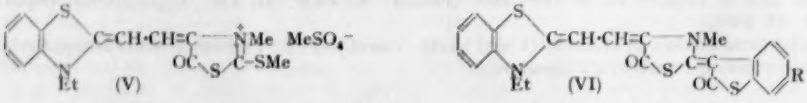
Parts I and II of this series * describe the preparation of *mero*cyanines which all contain the thio-oxindole nucleus linked in the 3-position to suitable heterocyclic systems but differ in the nature of the latter systems, in the nature and length of the connecting chain, and in the degree of substitution of the thionaphthen ring. As many of these compounds proved to be active photographic sensitisers, the preparation and properties of some trinuclear *mero*cyanines containing the thio-oxindole nucleus have now been examined.

Kendall and Brooker discovered independently (Mees, "The Theory of the Photographic Process," Macmillan, London, 1942, pp. 1037—1040) that a *mero*cyanine containing the rhodanine nucleus, *e.g.*, 3-ethyl-5-(3-ethylbenzothiazolin-2-ylidene-ethylidene)-2-thiothiazolid-4-one (I), may be quaternised with, for example, dimethyl sulphate, to give a



quaternary salt (II) which on treatment with a suitable cyclic ketomethylene compound forms a complex *mero*cyanine (III). Trinuclear dyes of the latter type are also photographic sensitisers.

We find that in the presence of a basic catalyst the deep red intermediate (II), in ethanol, readily condenses with thio-oxindole, at room temperature, with evolution of methanethiol and the formation of the deep purple dye (IV; R = H) in high yield. The use of 6-ethoxy(thio-oxindole) similarly affords the substituted dye (IV; R = OEt).

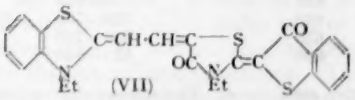


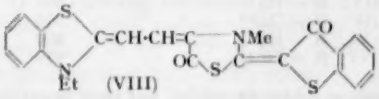
Knott and Jeffreys (*J.*, 1952, 4762) have recently shown that a series of reactions analogous to that of (I) → (III) may be carried out with *mero*cyanines derived from *iso*rhodanines (thiazolid-5-ones). Thus quaternisation of the *N*-methyl*iso*rhodanine analogue of (I) gives the salt (V) which with a ketomethylene compound forms a trinuclear *mero*cyanine. Using thio-oxindole we have thus obtained the deep blue *mero*cyanine (VI; R = H) and from 6-ethoxy(thio-oxindole) the ethoxy-derivative (VI; R = OEt).

For comparative purposes we prepared the thioindoxyl analogues of (IV and VI; R = H), *i.e.*, (VII) (cf. Kendall, B. P. 487,051/1936) and (VIII). These are less soluble in ethanol and acetone than their thio-oxindole isomers.

* Parts I and II, *J.*, 1952, 2135, 5012.

The absorption maxima of the new *iso*rhodanine dyes lie at appreciably longer wavelengths than those of the corresponding rhodanine compounds (cf. Knott and Jeffreys, *loc. cit.*). Thus, in 2-ethoxyethanol, (IV; R = H) has $\lambda_{max.}$ 577 mμ and (VI; R = H) $\lambda_{max.}$ 600 mμ; replacement of the thio-oxindole nucleus by that of thioindoxyl results in a bathochromic shift, *e.g.*, (VII) has $\lambda_{max.}$ 583 mμ, and (VIII) has $\lambda_{max.}$ 615 mμ; a


(VII)


(VIII)

similar effect is observed in the dimethin*mero*cyanines [cf. Glauert and Mann, *J.*, 1952, 2135; Kiprianov and Timoshenko, *Zhur. obshchey Khim.*, 1947, **17**, 1468; *Chem. Abs.*, 1948, **42**, 8475].

The absorption and sensitisation data are briefly summarised below.

Experimental

*Quaternised Dimethin*mero*cyanines.*—The dimethin*mero*cyanine was fused with methyl sulphate (2—4 mols.) at 130—135° for 15—30 min. The metho(methyl sulphate) was dissolved in warm methanol and precipitated by the addition of ether. The crystalline products were used without further purification.

3-Ethyl-(3-ethylbenzothiazolin-2-ylidene-ethylidene)-2-methylthio-4-oxothiazolonium methosulphate (II) formed crystals with a brown reflex, m. p. 207—208°; van Dormael (*Bull. Soc. chim. Belg.*, 1949, **58**, 403) gives m. p. 210—213°.

4-(3-Ethylbenzothiazolin-2-ylidene-ethylidene)-3-methyl-2-methylthio-5-oxothiazolonium methosulphate (V) separated as a red microcrystalline powder, m. p. 179° (decomp.), which, recrystallised from methanol–ether, gave the *hydrate*, small magenta needles, m. p. 194—196° (decomp.) (Found: C, 42·7; H, 4·5; N, 5·7. $C_{17}H_{20}O_5N_2S_4,H_2O$ requires C, 42·7; H, 4·6; N, 5·9%).

Trinuclear mero*Cyanines.*—A solution of the quaternised *mero*cyanine and the thio-oxindole or thioindoxyl (1 mol.) in warm ethanol was cooled to 25—30°, some crystallisation occurring. Triethylamine (1 mol.) was quickly added, and the mixture stirred and set aside overnight. Methanethiol was steadily evolved and the mixture darkened rapidly as the dye separated. The dye was collected, washed with a small quantity of ethanol, then with much water and again ethanol, and recrystallised by dissolution in a minimum of warm pyridine and addition of a tenfold volume of methanol.

3-Ethyl-5-(3-ethylbenzothiazolin-2-ylidene-ethylidene)-2-(2 : 3-dihydro-2-oxothionaphthen-3-ylidene)thiazolid-4-one (IV; R = H) formed small dark purple rods (72%), m. p. 221—222°, when inserted at 205° (Found: C, 62·15; H, 4·0; N, 5·8. $C_{24}H_{20}O_2N_2S_3$ requires C, 62·0; H, 4·3; N, 6·0%).

The *6-ethoxy*-derivative (IV; R = OEt) formed flat dark purple plates (77%), m. p. 226—227° with softening at 200° (Found: C, 61·85; H, 5·0; N, 5·8. $C_{26}H_{24}O_3N_2S_3$ requires C, 61·4; H, 4·75; N, 5·5%).

4-(3-Ethylbenzothiazolin-2-ylidene-ethylidene)-2-(2 : 3-dihydro-2-oxothionaphthen-3-ylidene)-3-methylthiazolid-5-one (VI; R = H) formed a *monohydrate* (78%), olive-green needles with golden reflex, m. p. 236—237° (Found: C, 58·8; H, 4·15; N, 6·2. $C_{23}H_{18}O_2N_2S_3,H_2O$ requires C, 58·95; H, 4·3; N, 6·0%).

The *6-ethoxy*-derivative (VI; R = OEt) separated as green prismatic needles (68%), m. p. 257—258° (inserted at 240°) (Found: C, 60·4; H, 4·5; N, 5·5. $C_{25}H_{22}O_3N_2S_3$ requires C, 60·7; H, 4·5; N, 5·7%).

3-Ethyl-5-(3-ethylbenzothiazolin-2-ylidene-ethylidene)-2-(2 : 3-dihydro-3-oxothionaphthen-2-ylidene)thiazolid-4-one (VII) formed green prisms (58%), m. p. 301—303° (Found: C, 62·1; H, 4·7; N, 6·3. $C_{24}H_{20}O_2N_2S_3$ requires C, 62·0; H, 4·3; N, 6·0%).

4-(3-Ethylbenzothiazolin-2-ylidene-ethylidene)-2-(2 : 3-dihydro-3-oxothionaphthen-2-ylidene)-3-methylthiazolid-5-one (VIII) formed blue-green prisms (46%) (from pyridine), m. p. 282—283° with previous softening (Found: C, 61·0; H, 4·4; N, 6·4. $C_{23}H_{18}O_2N_2S_3$ requires C, 61·3; H, 4·0; N, 6·2%).

We are greatly indebted to Imperial Chemical Industries Limited, Dyestuffs Division, for

the following report on the optical data of the *mero*cyanines and for the gift of intermediate compounds.

" The absorption values were determined in 2-ethoxyethanol solution. The *mero*cyanines (IV; R = H) and (VI; R = H) show quite good, although broad, sensitising action in

Compound	Absorption max. (mμ)	Sensitising max. (mμ)	Sensitising range (mμ)
(IV; R = H)	577	620	525—695
(IV; R = OEt)	576	620	520—700
(VI; R = H)	600	630	520—730
(VI; R = OEt)	610	600	525—740

positive (chlorobromide), but poor sensitisation in negative emulsions. The ethoxy-derivatives are inferior in both these respects to the corresponding unsubstituted compounds."

We gratefully acknowledge a grant provided by the Department of Scientific and Industrial Research (to A. J. W.).

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, September 2nd*, 1954.]

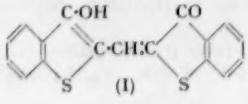
Some Oxonols derived from Thio-oxindole. Part I.

By R. H. GLAUERT, FREDERICK G. MANN, and A. J. WILKINSON.

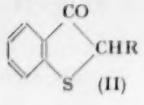
[Reprint Order No. 5697.]

The symmetrical oxonol derived from thio-oxindole and three unsymmetrical oxonols containing this nucleus have been prepared and their sensitising properties determined. Two of the latter dyes show abnormal behaviour on heating, undergoing isomerisation at their melting points.

BIS-[2-(2 : 3-DIHYDRO-3-OXOTHIONAPHTHEN)]METHINOXONOL (I) was first prepared by Friedländer and Kielbasinski (*Ber.*, 1911, **44**, 3098) who condensed thioindoxyl (II; R = H) with its 2-formyl derivative (II; R = CHO) in the presence of sulphuric acid. It has subsequently been obtained by the reaction of thioindoxyl with chloroform and alkali (Friedländer and Risse, *Ber.*, 1914, **47**, 1919), with formic acid (Schwenk, *J. pr. Chem.*, 1921, **103**, 103; Rodionov, Bogoslovskiĭ, and Kazakova, *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk*, 1948, 536; *Chem. Abs.*, 1949, **43**, 2200), and with formamide (Hünig, *Annalen*, 1951, **574**, 99). It is also formed by the interaction of thioindoxyl with thioindoxyl-2-aldehyde anil (II; R = ·CH:NPh) under acid conditions [Sveshnikov and Levkoev, *J. Gen. Chem.* (*U.S.S.R.*), 1940, **10**, 274]. Dyes of type (I) have been found



(I)



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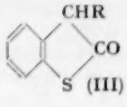

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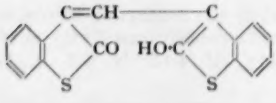

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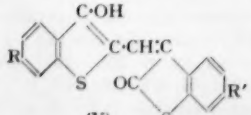


(V)

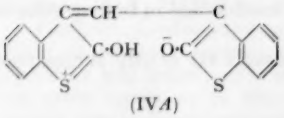
to act as photographic sensitisers for the green portion of the spectrum (Brooker, in Mees, " The Theory of the Photographic Process," Macmillan, London, 1942, p. 990). In view of the marked sensitising action of certain *mero*cyanines derived from thio-oxindole (Glauert and Mann, *J.*, 1952, 2135) it was of interest to prepare the isomeric oxonol (IV) containing two thio-oxindole nuclei, and unsymmetrical oxonols of type (V) containing one thioindoxyl and one thio-oxindole nucleus.

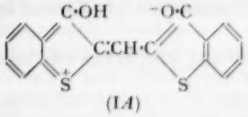
We have prepared the bright red bis-[3-(2 : 3-dihydro-2-oxothionaphthen)]methinoxonol (IV) by condensing thio-oxindole (III; R = H) with its 3-formyl derivative (III;

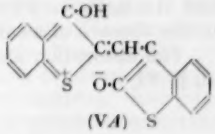
R = CHO) in the presence of triethylamine. Thio-oxindole-3-aldehyde anil (III; R = ·CH:NPh) failed however to react with thio-oxindole despite the use of a variety of conditions, and the attempted preparation of (IV) from thio-oxindole and formamide was also unsuccessful although under comparable conditions thioindoxyl gives an almost quantitative yield of the dye (I) (Hünig, *loc. cit.*).

The oxonol (V; R = R′ = H) was prepared by condensing thioindoxyl-2-aldehyde anil with thio-oxindole under acid or basic conditions: it could not be obtained by the condensation of thio-oxindole-3-aldehyde with thioindoxyl or by that of thio-oxindole with thioindoxyl and formamide. The deep red crystals melt at 222—223°, resolidify on further heating and remelt at 260—275°; the significance of this behaviour is discussed below.

The symmetrical oxonol (IV) derived from thio-oxindole is markedly more soluble in common solvents than the unsymmetrical dye (V) or the thioindoxyl compound (I); moreover, its absorption maximum, 500 mμ, is at much shorter wave-length than that of (V), $\lambda_{max.}$ 566 mμ, or of (I), $\lambda_{max.}$ 592 mμ. These properties may reflect (*a*) the greater degree of steric hindrance in (IV) preventing coplanarity of the two nuclei (cf. Knott, *J.*, 1952, 2399), and (*b*) the absence of *ortho*-quinonoid forms analogous to (I*A*) and (V*A*)- in bipolar structures, such as (IV*A*), which must contribute to the resonance hybrid of (IV).

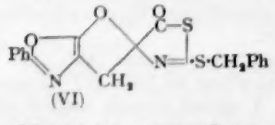

(IV*A*)

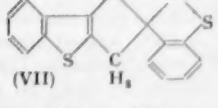

(I*A*)

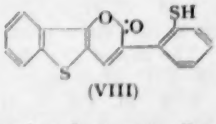

(V*A*)

The compound formed from (V; R = R′ = H) by the action of heat is an isomer, m. p. 283—284°: its ultra-violet spectrum in dioxan shows $\lambda_{max.}$ 370 mμ, and its infra-red spectrum shows no hydroxyl band. It is insoluble in aqueous alkalis but dissolves in hot ethanolic potassium hydroxide to give a yellow solution which on acidification yields a new compound, m. p. 159°, which in ethanol has $\lambda_{max.}$ 356 mμ, and which contains a hydroxyl group (band at 3·06 μ). This compound is reconverted at its melting point into the above isomer from which it appears on analytical evidence to be derived by addition of one equivalent of ethanol. Neither the compound of m. p. 283—284° nor that of m. p. 159° contains a thiol or a carboxylic acid group.

A satisfactory explanation of the above results has not been found. It may be noted that Knott (*loc. cit.*) has observed a somewhat similar but readier isomerism in some oxonols derived from oxazolones, and has suggested the spiran structure (VI) for the isomer of [2-benzylthio-4-thiazol-5-one][2-phenyl-4-oxazol-5-one]methinoxonol. It is unlikely that the isomer of (V; R = R′ = H) has the analogous structure (VII), for this


(VI)

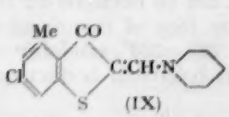

(VII)


(VIII)

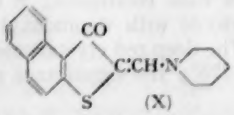
would not be expected to cause absorption at 370 mμ, and it also does not offer a satisfactory interpretation of the reaction with ethanolic potassium hydroxide. A further possibility that the isomer is the *o*-mercaptophenylthionaphthenopyrone (VIII) is precluded by the absence of a thiol group, although such a compound would be expected to undergo ring opening with alkali, with generation of hydroxyl group, and ready recyclisation. The molecular weight of the isomer indicates further that it is not the disulphide corresponding to (VIII). The exact structures of the isomer and its derived product remain obscure, and the small quantities available have prevented a fuller investigation.

We have also prepared oxonols of type (V) with an ethoxy-substituent in either the

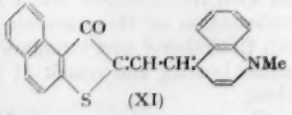
thio-oxindole or the thioindoxyl ring. The former dye (V; R = H, R′ = OEt) behaved like (V; R = R′ = H), undergoing isomerisation at its melting point; the latter, (V; R = OEt, R′ = H), however, did not. As the effect of the ethoxy-group in the second case will probably be to suppress the ionisation of the hydroxyl group of the thioindoxyl ring, the result suggests that ionisation of this group is the first stage in the observed isomerisation reaction.



(IX)



(X)



(XI)

The attempted condensation of 6-chloro-4-methylthioindoxyl-2-aldehyde and thio-oxindole in boiling ethanol containing piperidine gave mainly 6-chloro-4-methyl-2-(piperidinomethylene)thioindoxyl (IX), contaminated with a small amount of a red dye, presumably the required oxonol (as V). It was found moreover that the compound (IX) could be prepared by the direct reaction of the aldehyde and piperidine in ethanol. The fact that compounds of type (IX) can act as intermediates in the preparation of *mero*-cyanines from hydroxy-aldehydes in the presence of piperidine, as well as in the preparation of oxonols, has been shown by the preparation of the known *mero*cyanine (XI) (Glauert and Mann, *loc. cit.*) by the condensation of (X) and lepidine methiodide in boiling ethanol in the absence of a catalyst.

The absorption and sensitising properties of the new oxonols are briefly summarised on p. 33.

Experimental

Thio-oxindole, its 3-aldehyde, and the aldehyde anil were prepared by Glauert and Mann's method (*J.*, 1952, 2127).

Bis-[3-(2 : 3-*dihydro*-2-*oxothionaphthen*)]*methinoxonol* (IV).—A solution of thio-oxindole-3-aldehyde (III; R = CHO) (0·5 g.) and thio-oxindole (0·42 g., 1 mol.) in ethanol (10 c.c.) containing triethylamine (0·4 c.c., 1 mol.) was boiled for 3 hr. under reflux and the solvent then evaporated. The residual red gum was stirred and washed with ether (4 × 10 c.c.), and then dissolved in a minimum of hot acetic acid. The *oxonol* (IV) slowly crystallised in red needles, m. p. 162—163°, when recrystallised from acetic acid (Found: C, 65·6; H, 3·5. $C_{17}H_{10}O_3S_2$ require C, 65·8; H, 3·2%): 12%.

[2-(2 : 3-*Dihydro*-3-*oxothionaphthen*)][3-(2 : 3-*dihydro*-2-*oxothionaphthen*)]*methinoxonols* (V).—Equimolecular amounts of the appropriate thioindoxyl-2-aldehyde anil and the thio-oxindole, dissolved in the minimum of boiling ethanol, were treated with triethylamine (1 mol.). After 0·5—2 hours' boiling, the dye was worked up as above, ready crystallisation occurring on addition of the acetic acid.

The *oxonol* (V; R = R′ = H) formed red needles (36%), m. p. 222—223°, when inserted at 210°, resolidifying on further heating to 230° and remelting at 260—275° (Found: C, 65·7; H, 2·95. $C_{17}H_{10}O_3S_2$ requires C, 65·8; H, 3·2%). The use of a small quantity of hydrochloric acid as catalyst in place of triethylamine gave the same product.

The *oxonol* (V; R = H, R′ = OEt) formed clusters of red-brown prisms (43%), m. p. 179—181° when inserted at 165°, resolidifying by 185° and remelting at 250—257° (Found: C, 64·5; H, 4·3. $C_{19}H_{14}O_3S_2$ requires C, 64·4; H, 4·0%). A second sample melted only when inserted at *ca.* 195—200°, resolidifying in 1 min. at this temperature and remelting at 250—257° (Found: C, 64·3; H, 4·4%). The infra-red spectra of the two samples were indistinguishable.

Condensation of 6-ethoxy(thioindoxyl) and *NN′*-diphenylformamidine in boiling ethanol (15 min.) gave 6-*ethoxy*(*thioindoxyl*)-2-*aldehyde anil* as orange-brown crystals, m. p. 144°, from *cyclo*hexane (Found: C, 69·0; H, 5·2. $C_{17}H_{15}O_2NS$ requires C, 68·6; H, 5·1%). The *oxonol* (V; R = OEt; R′ = H) formed chocolate-coloured crystals (34%), m. p. 206°, unchanged on further heating to 300° (Found: C, 64·5; H, 4·2. $C_{19}H_{14}O_3S_2$ requires C, 64·4; H, 4·0%).

Isomer of the Oxonol (V; R = R′ = H).—The oxonol (570 mg.) was heated in an oil-bath for 10 min. whilst the temperature was raised from 225° to 235°. The dye melted with mild effervescence and some yellowish oil formed in the upper part of the tube. The residue,

dissolved in hot glacial acetic acid (125 c.c.), on cooling deposited dark crystals (315 mg.), m. p. 270—273°, which when recrystallised from the same solvent gave purple-brown crystals, m. p. 276—278° (Found: C, 65·85; H, 3·0%). A dark impurity was removed by chromatography of a benzene solution of the product on alumina, and recrystallisation from ethanol then gave the *isomer* as pale fawn needles, m. p. 283—284° (Found: C, 65·8; H, 3·1%; *M*, cryoscopically in ethylene dichloride, 300. $C_{17}H_{10}O_2S_2$ requires C, 65·8; H, 3·2%; *M*, 310). Solutions of the product in ethanol or benzene were fluorescent. A solution in dioxan showed $\lambda_{max.}$ 370 mμ, (ε 23,900); 389 mμ, (ε 18,500). The infra-red spectrum showed a carbonyl band at 5·78 μ but no hydroxyl or thiol bands.

This isomer (80 mg.) was boiled with potassium hydroxide (1 g.) in ethanol (20 c.c.) for 2 min., giving a yellow-brown solution which, when cooled, diluted with water (40 c.c.), and acidified with dilute hydrochloric acid gave a fawn-coloured precipitate. Recrystallisation from ethanol–water and then ethanol gave a *compound* as very pale yellow crystals, m. p. 159°, when inserted at 150°, resolidifying and remelting at *ca.* 285° (Found: C, 64·2, 64·3; H, 4·6, 4·6. $C_{19}H_{16}O_3S_2$ requires C, 64·0; H, 4·5%. $C_{38}H_{30}O_6S_4$ requires C, 64·2; H, 4·3%). The ultra-violet spectrum in ethanol showed $\lambda_{max.}$ 356 mμ (ε 13,500), and in ethanol containing a small quantity of sodium hydroxide 402—405 mμ (ε 7380). The infra-red spectrum showed a hydroxyl band at 3·06 μ and a carbonyl band at 5·91 μ, but no thiol band.

Isomer of the Oxonol (V; R = H; R′ = OEt).—The oxonol was heated for 10 min. at 200—230° and the product worked up as above, giving very pale brown prisms with a dark reflex, m. p. 262—263°, apparently the *isomer* (Found: C, 64·0, 63·9; H, 3·45, 3·7. $C_{19}H_{14}O_2S_2$ requires C, 64·4; H, 4·0%). In dioxan solution it showed $\lambda_{max.}$ 378 (ε 28,900), 397 mμ (ε 22,900).

Attempted Condensation of 6-Chloro-4-methylthioindoxyl-2-aldehyde with Thio-oxindole.—When an ethanolic solution of equimolecular amounts of the aldehyde, thio-oxindole, and piperidine was boiled under reflux for 6 hr. and cooled, the precipitate consisted largely of grey-green lumps, m. p. 191—194°, contaminated with a trace of red material. Recrystallisation from aqueous acetic acid gave the dye (IX), m. p. 195—197°, undepressed on admixture with the following authentic compound.

6-Chloro-4-methyl-2-(piperidinomethylene)thioindoxyl (IX) was formed readily when an ethanolic solution of 6-chloro-4-methylthioindoxyl-2-aldehyde and piperidine (1 mol.) was boiled for 6 hr. The product (58%) separated on cooling and gave yellow needles, m. p. 200—202°, from ethanol (Found: C, 61·3; H, 5·4; N, 5·1. $C_{15}H_{16}ONCIS$ requires C, 61·3; H, 5·45; N, 4·8%).

Mixing an ethanolic solution of this compound with an ethanolic solution of 2 : 4-dinitrophenylhydrazine containing some hydrochloric acid caused the slow deposition of the 2 : 4-dinitrophenylhydrazone of 6-chloro-4-methylthioindoxyl-2-aldehyde, m. p. 257—258°, undepressed on admixture with an authentic sample.

2-(Piperidinomethylene)-4 : 5-benzothioindoxyl (X), similarly prepared (77%) from 4 : 5-benzothioindoxyl-2-aldehyde, formed sparkling yellow plates, m. p. 190—191° (Found: C, 73·0; H, 5·8; N, 5·0. $C_{18}H_{17}ONS$ requires C, 73·2; H, 5·8; N, 4·7%). The infra-red spectrum showed a carbonyl band at 6·1 μ, and no :NH band.

When an ethanolic solution of this compound and lepidine methiodide (1 mol.) was boiled for 7 hr., a deep green colour developed with deposition of the crystalline [2-(2 : 3-dihydro-3-oxo-4 : 5-benzothionaphthen)][4-(1 : 4-dihydro-1-methylquinoline)]dimethin*mero*cyanine (XI), m. p. 285—287°, unaffected on admixture with an authentic sample; it gave a turquoise-coloured ethanolic solution.

Absorption and Sensitisation Data.—In the following Table, columns 2, 3, and 4 give the absorption maxima of the oxonols in ethanol, 2-ethoxyethanol containing a small amount of methanolic sodium hydroxide, and 2-ethoxyethanol containing a small amount of hydrochloric acid, respectively. Column 5 gives the absorption maxima in a positive chlorobromide emulsion and column 6 the sensitisation range in this emulsion. Figures are in mμ.

Oxonol	Absorption maxima			Max. in emulsion	Range
(I)	592	587	482	600	470—655
(IV)	500	500	430	515	(470)—550
(V; R = R′ = H)	566	566	465	580	(465)—635
(V; R = H, R′ = OEt)	578	580	—	565	460—630
(V; R = OEt, R′ = H)	490, 512	550	482	600	(480)—645

In positive emulsions, the sensitising power of the first three oxonols decreases in the order (I) > (V; R = R′ = H) > (IV), in agreement with the expectation on steric grounds; that

of (V; R = H, R′ = OEt) is markedly less than that of (V; R = OEt, R′ = H). All show only low sensitisation in negative emulsions.

We are greatly indebted to Imperial Chemical Industries Limited, Dyestuffs Division, for the above investigation of the absorption and sensitisation of the oxonols, and to the Department of Scientific and Industrial Research for a grant (to A. J. W.).

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Olefinic Additions with Asymmetric Reactants. Part III. The Resolution and Addition Reactions of 3-Ethylhept-3-en-2-ol. A Partial Asymmetric Synthesis effected by Hydrogenation.*

By C. L. ARCUS and D. G. SMYTH.

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(±)-3-Ethylhept-3-en-2-ol has been resolved into its enantiomeric forms. Hydrogenation of the (−)-isomer gave (−)-3-ethylheptan-2-ol; this alcohol on oxidation yielded (+)-3-ethylheptan-2-one, which gave a (+)-semicarbazone (see I—IV). The (+)-ethylheptenol yielded a similar series of compounds having the opposite configurations. A partial asymmetric synthesis is effected by these reactions: a new centre of asymmetry is formed at $C_{(3)}$, with preponderance of one configuration, and the original centre at $C_{(2)}$ is rendered symmetrical. The mechanism and stereochemistry of hydrogenation are discussed; it is concluded that the asymmetric centre controls the conformation in which the molecule is adsorbed at the catalyst surface, and that the subsequent addition of hydrogen is asymmetric by reason of this circumstance.

The reactions of the ethylheptenol with bromine, bromine–sodium methoxide, thiolacetic acid, and toluene-ω-thiol have been investigated.

(±)-3-ETHYLHEPT-3-EN-2-OL (I), prepared by the reaction of 2-ethylhex-2-enal with methylmagnesium iodide, has been resolved into its enantiomeric forms by fractional crystallisation of the brucine salt of its hydrogen phthalate. The (+)-hydrogen phthalate, which gave the less soluble salt, was obtained optically pure; on hydrolysis with 5N-potassium hydroxide it yielded (−)-3-ethylhept-3-en-2-ol. A portion of this alcohol was reconverted into its hydrogen phthalate, the specific rotation of which was 10·5% less than that of the original ester; this racemisation is ascribed to the occurrence, to a small extent, of alkyl–oxygen fission during the alkaline hydrolysis (Arcus and Kenyon, *J.*, 1938, 1917). On correction of the observed rotations for this racemisation, the rotatory power of the optically pure alcohol is found to be:

λ	5893	5780	5461	4358	
$[\alpha]^{19}$	−2·09°	−2·14°	−2·16°	−2·80°	(homogeneous)
$[\alpha]^{20}_{5893}$	−14·3° (in CS_2);	$[\alpha]^{20}_{5893}$	−6·8° (in $CHCl_3$)		

Hydrogenation.—(−)-3-Ethylhept-3-en-2-ol, on hydrogenation in ethanol with Raney nickel catalyst, gave (−)-3-ethylheptan-2-ol (II); this compound on oxidation with chromic anhydride yielded (+)-3-ethylheptan-2-one (III) which gave a (+)-semicarbazone

$$\underset{\text{(I)}}{CH_3{\cdot}CH(OH){\cdot}CEt{:}CH{\cdot}C_3H_7} \longrightarrow \underset{\text{(II)}}{CH_3{\cdot}CH(OH){\cdot}CHEt{\cdot}CH_2{\cdot}C_3H_7} \longrightarrow \underset{\text{(III)}}{CH_3{\cdot}CO{\cdot}CHEt{\cdot}C_4H_9} \longrightarrow \underset{\text{(IV)}}{CH_3{\cdot}C(:N{\cdot}NH{\cdot}CO{\cdot}NH_2){\cdot}CHEt{\cdot}C_4H_9}$$

(IV). The (+)-ethylheptenol yielded a similar series of compounds having the opposite configurations. A preliminary note has appeared (*Chem. and Ind.*, 1954, 404).

* The papers by Abbott and Arcus (*J.*, 1952, 1515) and Arcus and Strauss (*ibid.*, p. 2669) are regarded as Parts I and II.

These reactions constitute a partial asymmetric synthesis : a new centre of asymmetry is formed at $C_{(3)}$, with preponderance of one configuration, and the original centre at $C_{(2)}$ is rendered symmetrical.

The (−)- and the (+)-ethylheptenol used were respectively 86% and 82% optically pure. The alcohol (II) and the ketone (III) are liquids and were purified by simple distillation; the separation of diastereoisomers or of optical isomers is unlikely during this process (there was no experimental indication of separation), whence the maximum possible optical purity of (III) (*i.e.*, that for 100% asymmetric synthesis) is identical with the optical purity of (I). The percentage asymmetric synthesis is therefore equal to (or greater than) the yield of optically pure semicarbazone obtained from the ketone (III), together with a correction for the optical purity of the original alcohol (I). After the first recrystallisation, the m. p. and rotatory power of the (+)-semicarbazone were constant upon further crystallisation; the (−)-semicarbazone on one recrystallisation had an equal negative rotation; the yields were respectively 65% and 52%, whence the percentage asymmetric synthesis is 76% and 63%.

(±)-3-Ethylhept-3-en-2-ol was hydrogenated to (±)-3-ethylheptan-2-ol, which was converted into the 4-diphenylylcarbamate; recrystallisation of this derivative gave one compound only. This result indicates that hydrogenation yields a single diastereoisomeric racemate : if the configurations at $C_{(2)}$ and $C_{(3)}$ are designated by *d*, *l*, and *d'*, *l'*, respectively, then either (*dd'* + *ll'*)- or (*dl'* + *ld'*)-3-ethylheptan-2-ol is formed. Thus, as inferred from the results obtained with the optically active ethylheptenols, the configuration existing at $C_{(2)}$ controls the formation of that at $C_{(3)}$.

Stereochemistry of the Hydrogenation.—Recrystallisation of the semicarbazone and 2 : 4-dinitrophenylhydrazone of 2-ethylhex-2-enal, and of (±)-2-ethyl-1-methylhex-2-enyl * 4-diphenylylcarbamate, yielded in each instance only one compound. (±)-3-Ethylhept-3-en-2-ol on oxidation gave (±)-3-ethylhept-3-en-2-one, the semicarbazone of which was similarly a single entity. It is concluded that 2-ethylhex-2-enal, 3-ethylhept-3-en-2-ol, and 3-ethylhept-3-en-2-one are each a single geometrical isomer, and that very probably the same geometrical configuration has been retained during the conversion of aldehyde into secondary alcohol, and of the latter into ketone. We are informed by the manufacturers (Messrs. British Industrial Solvents Limited) that the 2-ethylhex-2-enal is prepared by the self-condensation of *n*-butyraldehyde; a similar condensation of acetaldehyde yields crotonaldehyde, and Blacet, Young, and Roof (*J. Amer. Chem. Soc.*, 1937, **59**, 608) conclude that purified commercial crotonaldehyde consists solely of the *trans*-isomeride. It is probable, therefore, that the present compounds have the aldehyde group, and groups derived from it, *trans* to the *n*-propyl group.

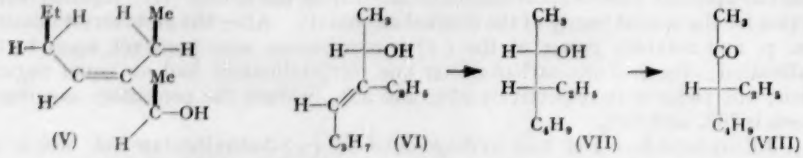
From a discussion of the stereochemistry of hydrogenation, Linstead, Doering, Davis, Levine, and Whetstone (*J. Amer. Chem. Soc.*, 1942, **64**, 1985) conclude, with regard to the " substrate " molecule, that the side which becomes attached to the metallic surface is, in general, that which conforms most closely to a plane, and that reaction proceeds by the addition of hydrogen atoms to this side of the molecule. The latter condition implies *cis*-hydrogenation; von Wessely and Welleba (*Ber.*, 1941, **74**, 777) have found *cis*-αβ-dimethylstilbene to give *meso*-βγ-diphenylbutane on hydrogenation, and the *trans*-compound, also *trans*-diethylstilbœstrol and its dimethyl ether, to yield the racemic dihydro-compounds; the configurations of these products are those which arise from *cis*-addition of hydrogen.

It is inferred that the most probable course for the hydrogenation of 3-ethylhept-3-en-2-ol is *cis*-addition at that side of the double bond which is adjacent to the nickel surface. Adsorption of the molecule most probably occurs by interaction of the lone-pairs of the oxygen atom, as well as of the π-electrons of the double bond, with the catalyst. A model of the ethylheptenol showed there to be one conformation of the molecule which conforms more closely to a plane than does any other, namely, that represented in (V). Conformation (V) has been adopted for the present discussion, but the mechanism proposed is not dependent on this particular conformation. The hydrogenation of (V) is represented in

* The alkyl radical derived from 3-ethylhept-3-en-2-ol is designated 2-ethyl-1-methylhex-2-enyl.

the Fischer formulæ (VI) and (VII), addition being to the surface of the paper; oxidation of (VII) yields 3-ethylheptan-2-one having configuration (VIII).

Finally, the implications of the steric course of the present hydrogenation may be summarised, without reference to particular configurations, as follows: Were adsorption, and hence addition, to occur with equal ease at either side of the double bond, then a single optical isomer of 3-ethylhept-3-en-2-ol would yield (±)-3-ethylheptan-2-one, and no asymmetric synthesis could result. Hence the asymmetric carbon atom must determine the configuration in which the molecule is adsorbed, *i.e.*, asymmetric adsorption precedes, and leads to, asymmetric addition of hydrogen.



An asymmetric synthesis effected by hydrogenation has been recorded by Vavon and Jakubowicz (*Bull. Soc. chim.*, 1933, **53**, 1111), who reduced the β-methylcinnamates of six optically active alcohols. Hydrolysis of the saturated esters yielded, in each instance, optically active β-phenylbutyric acid; the highest degree of asymmetric synthesis (20%) was obtained with the menthyl ester:

$$CMePh{:}CH{\cdot}CO_2R \longrightarrow CHMePh{\cdot}CH_2{\cdot}CO_2R \longrightarrow CHMePh{\cdot}CH_2{\cdot}CO_2H$$

Lipkin and Stewart (*J. Amer. Chem. Soc.*, 1939, **61**, 3295), in the hydrogenation of hydrocinchonine β-methylcinnamate, obtained 9% asymmetric synthesis.

Substantially less asymmetric synthesis occurs during the reduction of the β-methylcinnamic esters than in the present hydrogenations. This may be due to the separation of the ethylenic group from the asymmetric centre by two symmetrical atoms in the methylcinnamates; in 3-ethylhept-3-en-2-ol these structures are adjacent.

Reaction at a metal surface may also have occurred in an asymmetric synthesis which is not a hydrogenation. The Reformatsky reaction (1) has been found by Reid and Turner

$$\underset{(R = \text{menthyl})}{COMePh + Br{\cdot}Zn{\cdot}CH_2{\cdot}CO_2R} \longrightarrow CMePh(OH){\cdot}CH_2{\cdot}CO_2R \longrightarrow CMePh(OH){\cdot}CH_2{\cdot}CO_2H \quad . \quad (1)$$

(*J.*, 1949, 3365; 1950, 3694) to yield β-hydroxy-β-phenylbutyric acid having a rotatory power approximately one-third that of the optically-pure acid. Metallic zinc (50% excess) was present throughout the reaction, and it is now suggested that much of the interaction, and particularly that leading to asymmetric synthesis, takes place at the zinc surface. The following mechanism would lead to a substantial degree of asymmetric synthesis: the molecule $Br^{-}{}^{+}Zn{\cdot}CH_2{\cdot}CO{\cdot}O{\cdot}C_{10}H_{19}$ is adsorbed at the zinc surface in a configuration determined by the menthyl group; for minimum energy of activation, a molecule of acetophenone has to approach with carbonyl, methyl, and phenyl groups in a definite relationship to the adsorbed molecule. The new asymmetric centre will then be formed with a preponderance of one configuration.

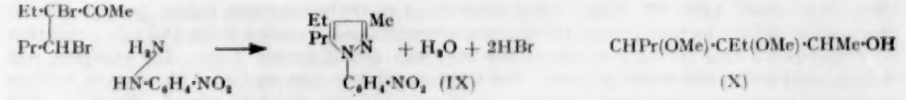
Other Addition Reactions.—Asymmetric syntheses have been effected by Kenyon and Partridge (*J.*, 1936, 1313) and Balfe, Kenyon, and Waddan (*J.*, 1954, 1366) through the addition of bromine to optically active pent-3-en-2-ol, 1-phenylbut-1-en-3-ol, and 1-phenylpent-1-en-3-ol, followed by oxidation of the dibromo-alcohol to the dibromo-ketone:

$$CHR{:}CR'{\cdot}CHR''{\cdot}OH \longrightarrow CHRBr{\cdot}CR'Br{\cdot}CHR''{\cdot}OH \longrightarrow CHRBr{\cdot}CR'Br{\cdot}COR''$$

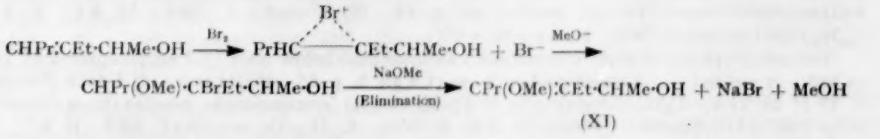
These reactions (R = Pr^n; R′ = Et; R″ = Me) have been applied to (+)-3-ethylhept-3-en-2-ol of 27% optical purity; the (+)-dibromo-alcohol on oxidation with chromic anhydride gave 3:4-dibromo-3-ethylheptan-2-one having a small positive rotation; on distillation it became practically optically inactive. This dibromo-ketone, and also that

prepared from the (±)-ethylheptenol, condensed with *p*-nitrophenylhydrazine to yield 4-ethyl-3-methyl-1-*p*-nitrophenyl-5-*n*-propylpyrazole (IX). It appears improbable that the compound is the isomeric 4-ethyl-5-methyl-1-*p*-nitrophenyl-3-*n*-propylpyrazole because this molecule, unlike (IX), cannot be formed by simple eliminations.

The stereochemical result of the bromine addition is inconclusive, and, in view of the difficulty in purification of the dibromo-ketone, a liquid racemising on distillation, and of preparing a solid derivative in the formation of which the dibromo-ketone does not undergo non-carbonyl reactions, the problem is somewhat intractable. Further addition reactions (below) have been investigated, but each potential asymmetric synthesis fails at some stage before the formation of a ketone.



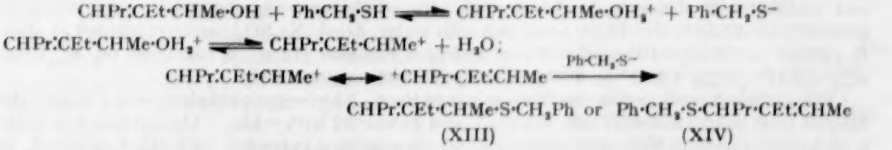
In an attempt to prepare the dimethoxy-alcohol (X), bromine was added to a solution of (±)-3-ethylhept-3-en-2-ol in methanolic sodium methoxide; there was obtained an unsaturated compound which gave analyses correct for an ethylmethoxyheptenol. This compound is most probably (±)-3-ethyl-4-methoxyhept-3-en-2-ol (XI), formed as follows:



The addition of thiolacetic acid to (±)-3-ethylhept-3-en-2-ol proceeded readily at 100° in the presence of benzoyl peroxide, and yielded (±)-4-acetylthio-3-ethylheptan-2-ol CHPr(SAc)·CHEt·CHMe·OH (XII). The acetylthio-group is considered to have added at the β-position to the carbinol group because such addition has been observed by Brown, Jones, and Pinder (*J.*, 1951, 2123) for the peroxide-catalysed reaction of allyl and 1-methylallyl alcohol with thiolacetic acid.

(XII)

The interaction of toluene-ω-thiol and (±)-3-ethylhept-3-en-2-ol yielded an unsaturated compound, containing no oxygen, which gave analyses correct for (±)-2-benzylthio-3-ethylhept-3-ene (XIII) or for the isomeric thioether (±)-4-benzylthio-3-ethylhept-2-ene (XIV). The occurrence of alkyl–oxygen fission during the hydrolysis of the hydrogen phthalate indicates the ethylmethylhexenyl group to have some capacity for separation as a carbonium ion, and the thio-ether is probably formed by an alkylation according to the following equations; the intermediate mesomeric cation may yield either (XIII) or (XIV):



Under the conditions above, thiolacetic acid added smoothly to 2-ethylhex-2-enal; by analogy with the addition of thiolacetic acid to other αβ-unsaturated aldehydes (Brown, Jones, and Pinder, *loc. cit.*), the acetylthio-group is considered to have combined at the β-carbon atom, giving 3-acetylthio-2-ethylhexanal CHPr(SAc)·CHEt·CHO.

Bromine added readily to the 2 : 4-dinitrophenylhydrazone of 2-ethylhex-2-enal, to yield that of 2 : 3-dibromo-2-ethylhexanal. The reaction demonstrates that 2-ethylhex-2-enal 2 : 4-dinitrophenylhydrazone has the assigned structure, and has not rearranged into the isomeric 1-(2 : 4-dinitrophenyl)-4-ethyl-5-*n*-propyl-Δ^2-pyrazoline.

Experimental

Rotations of undiluted liquid compounds are for *l*, 0·5; those of solutions are for *l*, 1·0.

A solution of 2-ethylhex-2-enal in ether was dried (Na_2SO_4) and distilled: the aldehyde had b. p. 65—66°/16 mm., n_D^{20} 1·4459. Its semicarbazone formed needles, m. p. 153° (Found: C, 58·9; H, 9·1; N, 22·9. Calc. for $C_9H_{17}ON_3$: C, 58·9; H, 9·3; N, 23·0%), from aqueous ethanol; Grignard and Fluchaire (*Ann. Chim.*, 1928, **9**, 17) record m. p. 147°. Its 2:4-dinitrophenylhydrazone formed orange plates, m. p. 124° (Found: C, 55·1; H, 5·9; N, 18·1. Calc. for $C_{14}H_{18}O_4N_4$: C, 54·9; H, 5·9; N, 18·3%), from acetic acid; Morgan and Hardy (*Chem. and Ind.*, 1933, 518) record m. p. 124—125°.

The ethylheptenol was prepared by a modification of Grignard and Vestermann's method (*Bull. Soc. chim.*, 1925, **37**, 425). To a solution of methylmagnesium iodide [prepared from magnesium (32 g.), methyl iodide (190 g.), and ether (300 ml.)], cooled in ice and salt, a solution of 2-ethylhex-2-enal (172 g.) in ether (200 ml.) was added during 2 hr. The complex was decomposed with ammonium chloride; the ethereal solution was washed with aqueous sodium hydrogen carbonate and with aqueous sodium hydrogen sulphite, dried (Na_2SO_4), and evaporated. The product, on distillation from potassium carbonate (1 g.), yielded (±)-3-ethylhept-3-en-2-ol (159 g.), b. p. 78—80°/15 mm., n_D^{20} 1·4490, d_4^{20} 0·845, $[R]_D$ 45·09 (Calc.: 44·82).

The ethylheptenol (1·0 g.) and 4-diphenylyl *iso*cyanate (1·25 g.) were heated for 3 hr. at 80°, and the product was extracted with light petroleum (b. p. 40—60°). The extract was chilled to −10°: a solid separated which, on recrystallisation, yielded (±)-*2-ethyl-1-methylhex-2-enyl 4-diphenylylcarbamate* (1·6 g.), needles, m. p. 74—75° (Found: C, 78·2; H, 8·1; N, 4·4. $C_{22}H_{27}O_2N$ requires C, 78·3; H, 8·1; N, 4·2%).

The ethylheptenol (2·0 g.) was oxidised as described below for (±)-3-ethylheptan-2-ol, but at 100°; it yielded (±)-*3-ethylhept-3-en-2-one* (1·8 g.), b. p. 65—66°/14 mm., n_D^{20} 1·4428 (Found: C, 77·2; H, 11·4. $C_9H_{16}O$ requires C, 77·1; H, 11·4%) [*semicarbazone*, needles (from ethanol), m. p. 180—181° (Found: C, 60·8; H, 9·6; N, 20·9. $C_{10}H_{19}ON_3$ requires C, 60·9; H, 9·7; N, 21·3%)].

Resolution of (±)-*3-Ethylhept-3-en-2-ol.*—This alcohol (132 g.) was kept for 6 hr. at 50° with phthalic anhydride (135 g.) and pyridine (85 g.); the viscous product was diluted with acetone, acidified with dilute hydrochloric acid, and poured on ice. The oil which separated was dissolved in ether; the solution was extracted with aqueous sodium hydrogen carbonate; the latter was acidified and extracted with ether; the extract was dried (Na_2SO_4) and evaporated by the passage of a stream of dry air, with final evaporation under reduced pressure: there was obtained (±)-*2-ethyl-1-methylhex-2-enyl hydrogen phthalate* (262 g.), a colourless oil (Found: equiv., 302. $C_{17}H_{22}O_4$ requires equiv., 290).

Brucine (308 g.) was cautiously added to a solution of the hydrogen phthalate (225 g.) in hot acetone (1 l.). Heating was continued until a clear solution was obtained, and, on cooling, the alkaloidal salt separated. After ten recrystallisations from acetone, the brucine salt (24 g.) of (+)-2-ethyl-1-methylhex-2-enyl hydrogen phthalate was obtained as rosettes of needles, m. p. 168—169°; the rotatory power of the hydrogen phthalate derived from the salt remained constant when this crop was subjected to two further recrystallisations. A total of 35 g. of the optically pure salt, $[\alpha]_{5893}^{20}$ −8·2° (*c*, 2·91 in $COMe_2$), was obtained; it was suspended in acetone and acidified with dilute hydrochloric acid; the whole was extracted with ether, which was washed with dilute hydrochloric acid, and with water, dried (Na_2SO_4), and evaporated as above. It yielded (+)-*2-ethyl-1-methylhex-2-enyl hydrogen phthalate* (14 g.), a colourless oil, n_D^{20} 1·5060, α_{5893}^{20} +8·41°, $[\alpha]_{5893}^{20}$ +18·1° (*c*, 4·19 in $CHCl_3$) (Found: equiv., 294).

The mother-liquors rich in the brucine salt of the (−)-hydrogen phthalate were concentrated, filtered from solid alkaloidal salt, acidified, and extracted with ether. The extract was shaken with aqueous sodium hydrogen carbonate, which was then extracted with ether, acidified, and again extracted. This last extract yielded (−)-2-ethyl-1-methylhex-2-enyl hydrogen phthalate (9 g.), having $[\alpha]_{5893}^{18}$ −17·6° (*c*, 2·61 in $CHCl_3$).

The (+)-hydrogen phthalate (14 g.) was heated under reflux with 5N-potassium hydroxide (25 ml.) for ½ hr. at 100°. Steam-distillation yielded (−)-3-ethylhept-3-en-2-ol (6·8 g.), b. p. 80—81°/15 mm., n_D^{20} 1·4497, d_4^{20} 0·845, α_{5893}^{19} −0·79°, α_{5780}^{19} −0·81°, α_{5461}^{19} −0·82°, α_{4358}^{19} −1·06°; $[\alpha]_{5893}^{20}$ −12·8° (*c*, 3·05 in CS_2); $[\alpha]_{5893}^{20}$ −6·1° (*c*, 2·46 in $CHCl_3$). A portion of the alcohol was reconverted into the hydrogen phthalate, which had $[\alpha]_{5893}^{20}$ +16·2° (*c*, 4·11 in $CHCl_3$).

Similar hydrolysis of the (−)-hydrogen phthalate (9 g.) yielded (+)-3-ethylhep-3-en-2-ol (3·8 g.), b. p. 81—82·5°/16 mm., α_{5893}^{19} +0·75°, $[\alpha]_{5893}^{20}$ +12·4° (*c*, 3·05 in CS_2).

Hydrogenation of 3-*Ethylhept*-3-*en*-2-*ol*.—A solution of (±)-3-ethylhept-3-en-2-ol (11·5 g.) in ethanol (100 ml.) was stirred with Raney nickel (4 g.); hydrogen was supplied, and the autoclave heated. Maximum temperature and pressure, 130° and 170 lb./sq. in., were attained after 4 hr.; the whole was then allowed to cool. The ethanolic solution yielded (±)-3-*ethylheptan*-2-*ol* (8·2 g.), b. p. 91—92°/22 mm., n_D^{20} 1·4308 (Found: C, 74·9; H, 13·9. $C_9H_{20}O$ requires C, 75·0; H, 13·9%). It did not decolorise a solution of bromine in carbon tetrachloride; each product from the attempted addition reactions (below) was so tested for unsaturation.

The ethylheptanol (0·5 g.) and 1-naphthyl *iso*cyanate (0·6 g.), heated at 100° for 1 hr., gave (±)-2-*ethyl*-1-*methylhexyl* 1-*naphthylcarbamate* (0·3 g.), needles, m. p. 48°, from light petroleum (b. p. 40—60°) (Found: C, 76·3; H, 8·5; N, 4·6. $C_{20}H_{27}O_2N$ requires C, 76·6; H, 8·7; N, 4·5%).

The ethylheptanol (3·0 g.) and 4-diphenylyl *iso*cyanate (4·2 g.) were similarly heated; the product was extracted with light petroleum and gave a carbamate (6·9 g.) which was four times recrystallised by chilling its solution in light petroleum (b. p. 40—60°) to −15°. It yielded (±)-2-*ethyl*-1-*methylhexyl* 4-*diphenylylcarbamate* (3·9 g.), needles, m. p. 103° (Found: C, 78·2; H, 8·6; N, 4·0. $C_{22}H_{29}O_2N$ requires C, 77·9; H, 8·6; N, 4·1%); there was no indication of the presence of an isomeric urethane.

During ½ hr., chromic anhydride (0·95 g.) was added portionwise with shaking to a solution of (±)-3-ethylheptan-2-ol (2·0 g.) in glacial acetic acid (5 ml.) at 80°. The whole, after cooling, was poured into water and extracted with ether. The extract was washed with aqueous sodium carbonate and dried (Na_2SO_4); it yielded (±)-3-*ethylheptan*-2-*one* (1·6 g.), b. p. 66°/16 mm., n_D^{20} 1·4206 (Found: C, 76·2; H, 12·7. $C_9H_{18}O$ requires C, 76·0; H, 12·8%). The *semicarbazone*, needles, m. p. 86°, from ethanol, was prepared by keeping the reactants overnight at room temperature (Found: C, 60·6; H, 10·6; N, 20·8. $C_{10}H_{21}ON_3$ requires C, 60·3; H, 10·6; N, 21·1%).

(−)-3-Ethylhept-3-en-2-ol (8·8 g., freshly distilled, α_{5893}^{18} −0·76°) was hydrogenated by the method described for the (±)-alcohol except that the maximum temperature and pressure were 96° and 109 lb./sq. in.; it yielded (−)-3-ethylheptan-2-ol (5·8 g.), b. p. 80—81°/12 mm., n_D^{20} 1·4312, d_4^{20} 0·821, α_{5893}^{19} −0·58°. Oxidation, as above, of the (−)-ethylheptanol (4·5 g.) gave (+)-3-ethylheptan-2-one (4·0 g.), b. p. 74—75°/16 mm., n_D^{20} 1·4211, α_{5893}^{19} +0·51°. The *semicarbazone*, needles (4·1 g.), derived from this ketone (3·5 g.) had m. p. 90—91°, $[\alpha]_{5893}^{19}$ +2·1° (*c*, 3·33 in $CHCl_3$); after recrystallisation from aqueous alcohol it (3·2 g.) had m. p. 91—92°, $[\alpha]_{5893}^{19}$ +2·2° (*c*, 3·93 in $CHCl_3$) (Found: C, 60·2; H, 10·8; N, 20·7%). Further recrystallisation resulted in no significant change in m. p. or specific rotation.

Hydrogenation (max. temp. and pressure: 120° and 140 lb./sq. in.) of (+)-3-ethylhept-3-en-2-ol (3·2 g., α_{5893}^{20} +0·72°) gave (+)-3-ethylheptan-2-ol (2·7 g.), b. p. 82—84°/16 mm., n_D^{20} 1·4310, α_{5893}^{20} +0·44°. The whole of this alcohol was oxidised, and yielded (−)-3-*ethylheptan*-2-*one* (1·8 g.), b. p. 73—75°/16 mm., n_D^{20} 1·4207, α_{5893}^{23} −0·31° (Found: C, 75·6; H, 12·3%). The *semicarbazone* (1·9 g.) prepared from this ketone (1·8 g.) had m. p. 86—89°, $[\alpha]_{5893}^{20}$ −2·1° (*c*, 3·33 in $CHCl_3$); after recrystallisation from aqueous alcohol it (1·3 g.) had m. p. 90—91°, $[\alpha]_{5893}^{20}$ −2·2° (*c*, 3·93 in $CHCl_3$) (Found: C, 60·4; H, 10·7; N, 20·9%).

Addition Reactions of 3-*Ethylhept*-3-*en*-2-*ol and* 2-*Ethylhex*-2-*enal*.—Bromine (3·45 g.) in chloroform (10 ml.) was added dropwise (½ hr.) to an ice-cooled solution of (±)-3-ethylhept-3-en-2-ol (3·0 g.) in chloroform (10 ml.). After the passage of a stream of dry air and final evaporation under reduced pressure, there remained (±)-3:4-dibromo-3-ethylheptan-2-ol (6·5 g.), a yellow oil, n_D^{20} 1·5121, which could not be distilled without decomposition. The dibromo-alcohol (6·5 g.), on oxidation with chromic anhydride (1·45 g.) at 70° by the method described for (±)-3-ethylheptan-2-ol, yielded (±)-3:4-*dibromo*-3-*ethylheptan*-2-*one* (5·9 g.), a lachrymatory yellow liquid, b. p. 72—74°/1 mm., n_D^{20} 1·5046 (Found: Br, 53·8. $C_9H_{16}OBr_2$ requires Br, 53·4%). The dibromo-ketone (1·5 g.), *p*-nitrophenylhydrazine (0·75 g.), and pyridine (1·0 g.) were heated for 3 hr. at 100°. The product was cooled, diluted with methanol, and poured into ice and dilute hydrochloric acid; the oil which separated solidified, and, after recrystallisation from aqueous acetic acid, gave 4-*ethyl*-3-*methyl*-1-p-*nitrophenyl*-5-n-*propylpyrazole* (0·3 g.), brown needles, m. p. 131° (Found: C, 66·7; H, 7·2; N, 15·6. $C_{15}H_{19}O_2N_3$ requires C, 66·2; H, 7·0; N, 15·4%).

By the above procedures, (+)-3-ethylhept-3-en-2-ol (2·2 g., α_{5893}^{20} +0·24°) yielded (+)-3:4-dibromo-3-ethylheptan-2-ol (4·6 g.), n_D^{20} 1·5158, $[\alpha]_{5893}^{20}$ +13·3° (*c*, 3·16 in CS_2), which gave 3:4-dibromo-3-ethylheptan-2-one: the undistilled ketone (4·1 g.) had n_D^{20} 1·5038, α_{5893}^{21} +0·11° (*c*, 3·36 in CS_2); after distillation it (3·4 g.) had b. p. 68—70°/0·2 mm., n_D^{20} 1·5034, α_{5893}^{20} −0·01°

(*c*, 3·46 in CS_2), and yielded the substituted pyrazole, m. p. 131° alone and when mixed with the analysed specimen.

Sodium (2·3 g.) was allowed to react with methanol (50 ml.; distilled from CaO), to which was then added (±)-3-ethylhept-3-en-2-ol (7·2 g.); after the dropwise addition of a solution of bromine (8·0 g.) in methanol (50 ml.), the whole was heated under reflux for 2 hr. It was poured into water and extracted with ether, which yielded (±)-*3-ethyl-4-methoxyhept-3-en-2-ol* (6·2 g.), b. p. 99°/24 mm., n_D^{20} 1·4444 (Found: C, 70·1; H, 11·4; Br, nil. $C_{10}H_{20}O_2$ requires C, 69·8; H, 11·5%).

(±)-3-Ethylhept-3-en-2-ol (2·0 g.) and thiolacetic acid (1·2 g.) were heated with a few mg. of benzoyl peroxide at 100° for 3 hr. The product on redistillation yielded (±)-*4-acetylthio-3-ethylheptan-2-ol* (2·3 g.), b. p. 86—87°/1 mm., n_D^{20} 1·4700 (Found: C, 60·4; H, 9·9; S, 14·5. $C_{11}H_{22}O_2S$ requires C, 60·5; H, 10·1; S, 14·7%).

(±)-3-Ethylhept-3-en-2-ol (2·0 g.) and toluene-ω-thiol (1·9 g.) were similarly heated for 5 hr.; fractionation of the product yielded (±)-*2-benzylthio-3-ethylhept-3-ene* (1·6 g.), b. p. 111°/1·5 mm., n_D^{20} 1·4820 (Found: C, 77·6; H, 9·6; S, 12·8. $C_{16}H_{24}S$ requires C, 77·5; H, 9·7; S, 12·9%).

2-Ethylhex-2-enal (2·0 g.) and thiolacetic acid (1·2 g.) were similarly heated for 4 hr. The product on redistillation gave *3-acetylthio-2-ethylhexanal* (2·0 g.), b. p. 79—80°/0·5 mm., n_D^{20} 1·4811 (Found: C, 59·0; H, 8·7; S, 16·0. $C_{10}H_{18}O_2S$ requires C, 59·3; H, 8·9; S, 15·9%) [2 : *4-dinitrophenylhydrazone*, yellow plates (from *cyclo*hexane), m. p. 80—81° (Found: C, 50·0; H, 5·8; N, 14·2; S, 8·3. $C_{16}H_{22}O_5N_4S$ requires C, 50·2; H, 5·8; N, 14·6; S, 8·4%)].

Bromine (0·35 g.) in chloroform (5 ml.) was added dropwise during 10 min. to a solution of 2-ethylhex-2-enal 2 : 4-dinitrophenylhydrazone (0·5 g.) in chloroform (20 ml.). The solvent was evaporated under reduced pressure; the product, on recrystallisation from *cyclo*hexane, yielded 2 : *3-dibromo-2-ethylhexanal* 2 : *4-dinitrophenylhydrazone* (0·4 g.), yellow needles, m. p. 131—132° (Found: C, 36·1; H, 3·8; N, 11·6; Br, 34·6. $C_{14}H_{18}O_4N_4Br_2$ requires C, 36·1; H, 3·9; N, 12·0; Br, 34·3%).

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Kinetic Features of the Oxidation of Aldehydes, Ketones, and Nitroparaffins with Alkaline Ferricyanide.

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Reaction orders have been determined for the oxidation of three aldehydes, four ketones, and two nitroparaffins by alkaline ferricyanide. Oxidation occurs only after these substances have been converted into the anions of their enolic or aci-forms. The reacting systems do not catalyse vinyl polymerisation and it is concluded that the oxidisable anions form complexes with $[Fe(CN)_6]^{3-}$ and are then attacked by more ferricyanide.

SINCE the system * Red. + $\{Fe(CN)_6\}^{3-} \rightleftharpoons$ Ox. + $\{Fe(CN)_6\}^{4-}$ involves one-electron transfer, free radicals are probable intermediates in oxidations of organic compounds by potassium ferricyanide, but there is very little experimental evidence that this is indeed the case. Oxidation of phenol by alkaline ferricyanide has been explained on this basis and a coloured free radical has been produced in this way from 2 : 4 : 6-tri-*tert.*-butylphenol (Cook and Woodworth, *J. Amer. Chem. Soc.*, 1953, **75**, 6242). Again, production of the dimer $(Me_2C{\cdot}NO_2)_2$, though only in 6—15% yield, in the oxidation of 2-nitropropane has been ascribed to the formation of a transient radical intermediate (Schlechter and Kaplan, *ibid.*, p. 3980). To obtain more definite information concerning the possible

* Red. = a reducing agent and Ox. = an oxidising agent, and braces are used to delineate complex ions so as to avoid confusion with the more usual square brackets, which in this paper are required later to denote concentrations.

participation of organic free radicals in oxidations of simple organic compounds by aqueous alkaline ferricyanide we have carried out a kinetic investigation of its oxidising actions on propanal, butanal, and *iso*butanal, on dimethyl, diethyl, di*iso*propyl, and ethyl methyl ketones, and also on nitroethane and 2-nitropropane. From its outcome we have been forced to conclude that though the oxidation proceeds in several consecutive stages the expected *free* radicals of the above-named substances have no independent existence under our experimental conditions. We have found, significantly, that the diagnostic test of catalysis of vinyl polymerisation, which can be exhibited by oxidations of these same compounds with manganic pyrophosphate (Drummond and Waters, *J.*, 1953, 2836), is negative with all the ferricyanide oxidations which we have as yet examined under a nitrogen atmosphere, and the rate of reduction of $\{Fe(CN)_6\}^{3-}$ is not changed by the addition of vinyl cyanide to the reacting mixtures. However, if samples of the butanals which have been distilled in air, and therefore probably contain small amounts of peroxides, are used then some polymerisation of vinyl cyanide does occur at the outset of the reaction, but if, with these aldehydes, the vinyl cyanide is added after enough time has been allowed to permit the alkaline ferricyanide–ferrocyanide mixture to destroy any initial peroxide then there is no polymerisation. The absence of polymerisation cannot therefore be due merely to the use of an alkaline medium.

Very few quantitative studies of oxidations of organic compounds by alkaline ferricyanide have hitherto been made. The ferricyanide method of glucose estimation (Hagedorn and Jensen, *Biochem. Z.*, 1923, **135**, 46), later developed by Hawkins and Van Slyke (*J. Biol. Chem.*, 1929, **81**, 459) and by Hawkins (*ibid.*, 1929, **84**, 69, 78), does not give stoicheiometric end-points and requires careful control of pH, temperature, and reaction time. The volumetric procedure (Lang, *Z. anorg. Chem.*, 1924, **138**, 271) depending on the precipitation of a complex zinc ferrocyanide to complete the reaction

$$2\{Fe(CN)_6\}^{3-} + 2I^- \longrightarrow 2\{Fe(CN)_6\}^{4-} + I_2$$

gave results of poor reproducibility in our hands, probably because atmospheric oxidations could not altogether be prevented. Potentiometric measurements of the change with time of the [Ferricyanide]/[Ferrocyanide] ratio, used by Conant, Aston, and Tongberg (*J. Amer. Chem. Soc.*, 1930, **52**, 407) in an earlier survey of this subject, proved to be more reliable provided that only the initial stages of oxidations were followed and that care was taken both to work in a nitrogen atmosphere and to prevent the occurrence of any of the photochemical reactions of ferri- or ferro-cyanides.

After prolonged reaction some breakdown of both $Fe(CN)_6$ ions occurs and the oxidations do not appear to cease at any definite stage. Several equivalents of ferricyanide can eventually be consumed per mole of organic substance and, in particular, the oxidation of a normal aliphatic aldehyde does not yield merely the corresponding fatty acid. The complicated nature of this oxidation and the fact that aldehydes and ketones behave similarly was first stressed by Conant and Aston (*ibid.*, 1928, **50**, 2783) who from the oxidations of *iso*butanal and methyl *iso*propyl ketone with hot alkaline ferricyanide isolated dihydropyrazine derivatives and suggested that the attack started at the α-CH group of the system $R_2CH{\cdot}CO{\cdot}R'$.

Conant, Aston, and Tongberg (*loc. cit.*), who examined aldehyde oxidation more quantitatively, found that the more alkaline the solution the more rapid was the reaction, and, in accordance with Conant's contemporary views (Conant, *Chem. Reviews*, 1926, **3**, 1; Conant and Pratt, *J. Amer. Chem. Soc.*, 1926, **48**, 3178, 3220) concerning "apparent oxidation potentials," they considered that the initial stage of the oxidation of an organic substance by an electron-abstracting agent might be fast, reversible, and pH dependent; *i.e.*:

$$R{-}H - e \rightleftharpoons R\cdot + H^+ \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

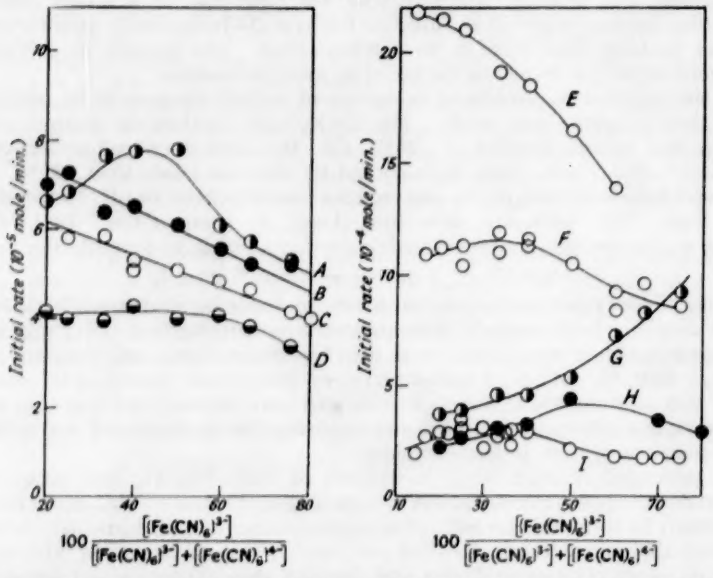
Consequently oxidation of a substance R–H would not be expected to set in until the redox potential of the equilibrium (1) fell below that of the pH-independent ferricyanide-ferrocyanide system. Though Conant, Aston, and Tongberg attempted to find reaction orders they invariably worked with mixtures initially containing equivalent amounts of ferri- and ferro-cyanide, for then, since $\Delta\pi = (\boldsymbol{RT}/\boldsymbol{F})\log(1 + s)/(1 - s)$, the potential drop

($\Delta\pi$) varies linearly with s (the fraction of ferricyanide reduced) for an appreciable portion of the reaction and the potential measurements can very simply be converted into reaction velocity constants. Had they worked with varying initial [Ferricyanide]/[Ferrocyanide] ratios they would have discovered that ferrocyanide anions do not retard the oxidations of aldehydes or ketones, as would be the case if the reaction process had a reversible first stage (1), or better (2):

$$R\text{-}H + \{Fe(CN)_6\}^{3-} \rightleftharpoons R\cdot + H^+ + Fe(CN)_6^{4-} \quad . \quad . \quad . \quad . \quad . \quad (2)$$

With all our substrates the initial rate of reaction is somewhat dependent upon the [Ferricyanide]/[Ferrocyanide] ratio, as Fig. 1 shows, but the change is usually quite small and may be due to salt effects or complex formation.

FIGS. 1*a and b*. *Variation of the initial oxidation rate with the ratio* $\frac{[\{Fe(CN)_6\}^{3-}]}{[\{Fe(CN)_6\}^{3-}]+[\{Fe(CN)_6\}^{4-}]}$



For. all Figs: *A*, Propanal. *B*, Di*iso*propyl ketone. *C*, Diethyl ketone. *D*, Ethyl methyl ketone. *E*, Acetone. *F*, *n*-Butanal. *G*, 2-Nitropropane. *H*, *iso*Butanal. *I*, Nitroethane.

For all except Fig. 1, graphs refer to results obtained with equimolar amounts of ferricyanide and ferrocyanide as oxidant.

Except in the case of *n*-butanal, the initial rate of oxidation is proportional to the hydroxyl-ion concentration of the solution (see Fig. 2), whilst in most cases the reaction order with respect to the organic substrate is also unity (see Fig. 3). The reaction order with respect to ferricyanide however is variable. The reaction is of zero order for *iso*butanal, of first order at low concentrations but tending to zero at high concentrations with *n*-butanal and diethyl ketone, and of first order with propanal, ethyl methyl ketone, di*iso*propyl ketone, and 2-nitropropane; with acetone and nitroethane it is of first order at low concentrations of ferricyanide but becomes of second order at higher concentrations (see Fig. 4). Consequently we are dealing with an oxidation in which no single reaction is regularly the rate-controlling process.

The alkali-dependence of the reaction indicates that the oxidised substances are not the aldehydes, ketones, or nitroparaffins themselves but the anions of their enolic or aci-forms. Enolisation prior to oxidation is thought to be necessary for the very similar

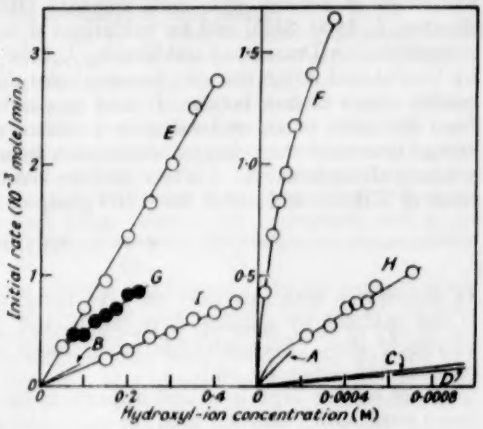


FIG. 2. *Variation of initial oxidation rate with hydroxyl-ion concentration.*

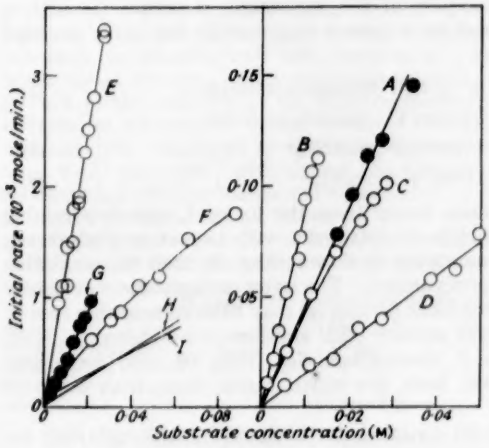
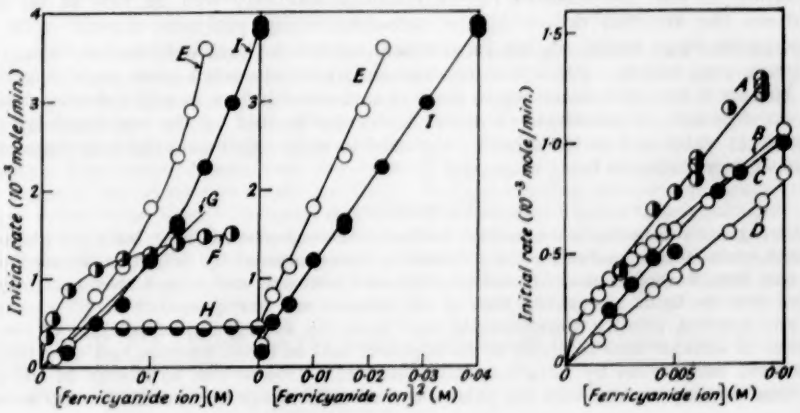


FIG. 3. *Variation of initial oxidation rate with substrate concentration.*

FIGS. 4*a* and *b*. *Variation of initial oxidation rate with ferricyanide-ion concentration.*



oxidations of ketones with ceric sulphate (Hinshelwood and Shorter, *J.*, 1950, **3276**; Shorter, *J.*, 1950, **3425**) and for oxidations of both aldehydes and ketones with manganic pyrophosphate (Drummond and Waters, *J.*, 1950, **3425**; 1955, in the press), but was rejected by Conant and Aston (*loc. cit.*) because *inter alia* one-electron abstracting agents do not readily attack olefinic bonds. It may be pointed out however that electron abstraction from the anion of an enol will give a mesomeric radical (I), and thus requires a lower energy increment than electron abstraction from a C–H bond or from the oxygen atom of a simple alkoxide anion. Further electron loss from (I) leads to oxidation at the α-carbon atom of ·CH·CO· and not at the ·CHO group of an aldehyde :

$$R_2C{=}C(O:)-R' \longleftrightarrow R_2\dot{C}-C(O:)-R' \xrightarrow{-e} R_2\overset{+}{C}-C(O)-R'$$
(I) (II)

In accordance with this view we have found that benzaldehyde, which cannot enolise, is not oxidised by alkaline ferricyanide and that the oxidation of furfuraldehyde is extremely slow. Formaldehyde too is much less easily oxidised than its homologues (Conant and Aston, *loc. cit.*).

Since no *free* organic radical appears to be formed we suggest that the ferricyanide anion must form a complex with the enolic anion of the substrate and this complex, which could equally well be described as a complex of the mesomeric structure (I) with a ferrocyanide anion, must then be attacked by a second ferricyanide ion (5) or perhaps by a similar complex (6); *i.e.*:

$$R\text{-}H + OH^- \rightleftharpoons R^- + H_2O \text{ (enolisation, reversible)} \quad (3)$$

$$R^- + \{Fe(CN)_6\}^{3-} \longrightarrow \text{Complex (X) (possibly reversible)} \quad (4)$$

$$X + \{Fe(CN)_6\}^{3-} \longrightarrow \text{Product} + 2\{Fe(CN)_6\}^{4-} \quad (5)$$

$$2X \longrightarrow \text{Dimer} + 2\{Fe(CN)_6\}^{4-} \quad (6)$$

If the reversible enolisation (3) is much faster than the forward, rate-determining reaction (4), then the total reaction should be of first order with respect to [Substrate], [OH^-], and [Ferricyanide], but if the enolisation is slower than (4) then the oxidation should be of zero order with respect to [Ferricyanide]. The latter circumstances evidently hold for *iso*butanal, whilst for *n*-butanal reactions (3) and (4) may have comparable speeds. The rates of (OH^-)-catalysed enolisations of acetone (Bell and Longuet-Higgins, *J.*, 1946, 636) and nitroethane (Maron and La Mer, *J. Amer. Chem. Soc.*, 1938, **60**, 2588) have been measured; at comparable concentrations both are much faster than their rates of oxidation as determined by us.

Apparently reactions (5) and perhaps (6) are much faster than (4); although they are bimolecular reactions between similarly charged ions they are probably highly exothermic. However with acetone, and perhaps with nitroethane, reaction (4) may reach an equilibrium so that (5) becomes rate-determining. It may well be that in all these oxidations the reaction orders of the rate-determining processes depend upon the concentration range examined, but for practical reasons we have been unable to vary our conditions very widely. For instance, since aldehydes are much more rapidly oxidised than ketones it has been necessary to work in carbonate buffers, in which slow enolisation is to be expected. Concentrations of substrates are limited on the one hand by their solubility in water and on the other by the need to ensure that only the first stage of the oxidative degradation is being examined.

Experimental

The organic substances were freshly distilled in nitrogen before use; with the aldehydes frequent fractionation was necessary. Solutions were prepared by weight in distilled water that had been flushed thoroughly with oxygen-free nitrogen, and a slow stream of nitrogen was led over the liquid whenever a flask of any solution was unstoppered.

Early reaction velocity measurements were made by adding aliquot portions of reacting mixtures at suitable time intervals to 2N-sulphuric acid to arrest reaction and then titrating the unused ferricyanide by Lang's method (*loc. cit.*). Trouble due to change of end-point with time was experienced with the aldehydes; on the average however the results accorded

with the potentiometric measurements sufficiently well to establish that the potential changes of the reacting solutions were indeed due to the reduction of ferricyanide.

Potentiometric measurements were carried out in a wide-mouthed blackened bottle immersed in a thermostat at 25° ± 0·2°. The stopper of the bottle carried a bright platinum electrode, a saturated calomel electrode, a glass stirrer and its bearing, an inlet tube for oxygen-free nitrogen, and a stoppered hole through which known volumes of reagents could be added. Measurements were made with a Tinsley potentiometer (Model No. 3184) and, except in the first 2 min., equilibrium between the solution and the electrodes was rapidly attained. Potentials were measured to 0·2 mv at intervals of 3 min. and plotted against time for 20—30 min. Reaction velocities were computed from these potential–time lines by Conant and Aston's method (*loc. cit.*), reference being made to the appropriate part of an experimentally determined potential curve for ferrocyanide–ferricyanide mixtures of comparable strength.

With the aldehydes in particular, the use of nitrogen was essential. In the presence of air the oxidations appeared to be preceded by an induction period before they set in, in most cases, at the same rate as in de-aerated solutions. This effect, we think, may be due to the presence, or formation, of peroxide which re-oxidises some ferrocyanide to ferricyanide and sometimes caused a slight initial potential increase. In a nitrogen atmosphere the potential drop indicative of oxidation of the organic substance starts immediately and continues at a steady rate until about 0·1 equiv. of the less concentrated reagent has been consumed.

Further to obviate photochemical decompositions (compare Asperger, *Trans. Faraday Soc.*, 1952, **48**, 617, and earlier papers) weighed quantities of pure potassium ferrocyanide and potassium ferricyanide were first dissolved in a known volume of distilled water in a dark bottle under nitrogen. Aliquots of this solution, of the alkaline buffer, and of an aqueous solution of the substrate at the same temperature were mixed, with stirring in a stream of nitrogen, in the reaction vessel, timing of the reaction being made from the instant of last addition. For oxidations of aldehydes carbonate–bicarbonate buffers (*ca.* 0·1M) in the pH range 9—11 were used; with ketones and nitroparaffins, sodium hydroxide solutions had to be used together with much more dilute solutions of the reactants. Values of [OH^-] were calculated from pH's measured with a Doran pH meter and an "alkacid" glass electrode, with correspondingly prepared reaction mixtures containing no organic substrate.

Some of our detailed findings are tabulated; see also the Figures.

pH *values for convenient study of the kinetics of oxidation.*

Acetone	13—13·5	Ethyl methyl ketone	10—11
Diethyl ketone	10—11	Di*iso*propyl ketone	12—13
Propanol	9—10	*n*-Butanal	10—10·5
*iso*Butanal	10—11	2-Nitropropane	12·5—13·5
Nitroethane	12·5—13·5		

Extent of possible oxidation: equivalents of ferricyanide consumed per equivalent of substrate after 3 weeks' reaction at 25°.

Acetone	13·2	Ethyl methyl ketone	11·0	Diethyl ketone	13·7
Di*iso*propyl ketone	10·7	Propanal	8·0	*n*-Butanal	11·9
*iso*Butanal	12·4	Nitroethane	11·8	2-Nitropropane	20·2

Tests for Free-radical Formation.—With all the substances named, tests for the catalysis of vinyl polymerisation were carried out in evacuated Thunberg tubes (Drummond and Waters, *loc. cit.*); all were negative. With *n*-butanal it was shown that neither vinyl cyanide nor methyl methacrylate affected the oxidation rate. Excess of vinyl acetate, if mixed with the alkaline ferricyanide for 40 min. before addition of the aldehyde, completely stopped its oxidation. Diminutions of rate were also observed with additions of nitrosobenzene (to 50%), ethyl acetate, and vinyl propionate (to 75%), and the reacting solutions then noticeably changed colour when kept. The vinyl esters are not hydrolysed under these conditions since this would have led to acetaldehyde formation and enhanced reduction of the ferricyanide. Since the additions of the above substances to already reacting mixtures caused no immediate change in the rate of potential variation the effects described above may be due to complex formation with the ferricyanide or ferrocyanide (cf. *J.*, 1953, 1041).

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The Dyson Perrins Laboratory, Oxford. [*Received, July 17th*, 1954.]

The Production of Active Solids by Thermal Decomposition. Part V. The Sintering of Active Magnesium Oxide.*

By S. J. Gregg, R. K. Packer, and K. H. Wheatley.

[Reprint Order No. 5576.]

Two series of experiments have been performed to test the reality of the sintering of active solids postulated in Part I (*J.*, 1953, 3940). In the first the starting material was pure precipitated magnesium hydroxide, and in the second a sample of active magnesium oxide prepared from the same hydroxide by calcining for six hours at 534°; separate samples of both starting materials were calcined for varying periods at a number of fixed temperatures and the specific surface, the heat of immersion, the density, and certain other properties of the cooled products examined. The results confirm that sintering does occur and that it is promoted by an increase in either time or temperature. They also indicate that sintering may be accompanied by progressive elimination of chemisorbed water (or of chemisorbed carbon dioxide for the older specimens) from the surface of the micelles. It is further shown that the " activation " of the solid may occur after the decomposition of the parent substance rather than simultaneously with it.

In Part I (*J.*, 1953, 3940) it has been postulated that active solids prepared by thermal decomposition of a parent substance at elevated temperatures begin to sinter as soon as they have been formed. The process of sintering should, from its very nature, depend on time as well as on temperature, so it was considered desirable to demonstrate directly, the progress of sintering with time. The solid chosen was magnesium oxide, as we had already acquired some knowledge on this substance (Gregg and Razouk, *J.*, 1949, S36; Britton, Gregg, and Winsor, *Trans. Faraday Soc.*, 1952, **48**, 63; Gregg and Packer, see Part VI, following paper). Separate samples were calcined for varying periods at fixed temperatures, and, on cooling, the content of volatile matter, the apparent density, the specific surface area, and, for certain samples, the heat of immersion were determined. The results show clearly the reality of the sintering, but that the problem is complicated and requires further study before a fully quantitative model can be formulated.

Experimental

Materials.—The magnesium hydroxide (Batch A), which is more fully described in Part VI, was prepared from the chloride by precipitation with aqueous ammonia. Its chloride-ion content was only 0·015%; its " water " content was 30·93 (Calc., 30·88%), and the specific surface area, measured by nitrogen sorption at −183°, was 56 $m.^2 g.^{-1}$.

Procedure.—The experiments fell into two separate Series. In Series I the starting material was magnesium hydroxide and separate samples were calcined for varying periods at 400°, 700°, and 750°, the products being examined on cooling. In Series II, carried out some months later, it was desired that the starting material should be such that any heat treatment it received would bring about no further activation but only sintering; accordingly a portion of the same batch of hydroxide as that used in Series I was first heated to 534° ± 5° for 6 hr. to become the starting material for Series II. (Preliminary experiments had shown that the rate of loss of weight after 6 hr. at this temperature was exceedingly slow.) Separate samples of this already calcined material were then further calcined on the thermal balance (Gregg and Winsor, *Analyst*, 1945, **70**, 336) for varying times at 534° ± 5°, 561° ± 5° and 592° ± 5°, and the products were examined after cooling.

Details of the tests employed have been, or will be, described elsewhere, *viz.*, specific surface by nitrogen sorption at −183° (Gregg and Sing, *J. Phys. Coll. Chem.*, 1951, **55**, 592); the apparent density ρ in carbon tetrachloride (*idem*, *ibid.*, 1952, **56**, 388); the heat of immersion

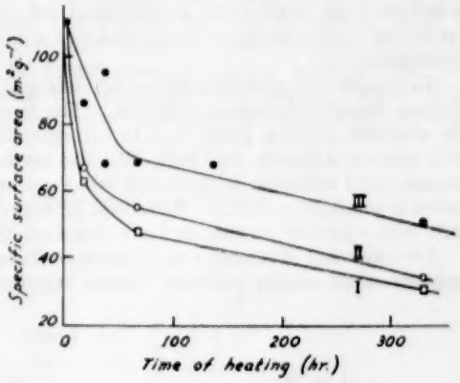
* Part IV, *J.*, 1954, 3887.

in carbon tetrachloride (Asher, Gregg, and Hill, unpublished work); content w of volatile matter, by heating the material to 980° on the thermal balance (Gregg and Hill, *J.*, 1953, 3945).

Results and Discussion

The results for Series II will be presented first. In Fig. 1 the specific surface area S is plotted against time; the points do not lie even approximately on a straight line, the rate of fall of S being far greater in the early stages than in the later. If, however, the quantity $1/S\rho(=r$, say) be plotted against the square root of the time the points, including

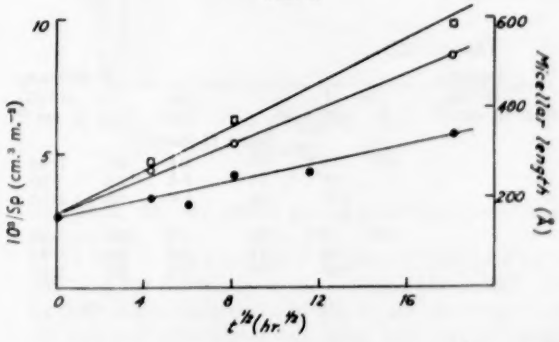
Fig. 1.



Figs. 1 and 2. *Effect of time of heating on the sintering of active magnesium oxide prepared by heating the precipitated hydroxide for 6 hours at 534°.*

I, 592°; II, 561°; III, 534°.

Fig. 2.



that for zero time, fit with some scatter along a straight line (Fig. 2). The quantity $S\rho$ is actually the surface area per $cm.^3$ of the solid material, so that $1/S\rho$ is essentially the ratio of the true volume to the surface area of the solid; it may perhaps be made more concrete by means of the simplifying (though obviously very crude) assumption that the material exists as equal cubelets, or micelles, of length l; for then $l = 6/S\rho$ and the use of the right-hand scale of Fig. 2 gives the rate of growth of micellar length with time. The equation to the straight lines may be written as

$$l - l_0 = kt^{\frac{1}{2}} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

or as

$$r - r_0 = 6kt^{\frac{1}{2}} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where l_0 is the micellar length, and r_0 is the value of the volume-to-surface ratio, at the commencement of the experiment, k being a constant at constant temperature. A

relationship identical with (1) is followed in the oxidation of certain metals with l as the thickness of the oxide layer; the resemblance is purely formal, however, for, whereas the oxide layer increases in thickness as a result of a net transport of matter (oxygen) from the outside, in sintering, the reduction is brought about by a mere rearrangement of material already present without any increase in the total quantity.

Differentiation of equations (1) and (2) gives

$$\mathrm{d}l/\mathrm{d}t = \tfrac{1}{2}kt^{-\frac{1}{2}} = \tfrac{1}{4}k^2/(l - l_0) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

and

$$\mathrm{d}r/\mathrm{d}t = k^2/[72(r - r_0)] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

respectively. These imply that the rate of increase in micellar length or in the volume-to-surface ratio is inversely proportional not, as might have been expected, to l or to r but rather to the ***change*** in each quantity which has occurred since the beginning of the experiment.

No simple and plausible model has emerged so far for the quantitative interpretation of these deceptively simple relations. The temperature range is so low when referred to the absolute melting point T_m—it corresponds to an α-value of some 0·25 only—that both surface diffusion and bulk diffusion seem to be ruled out and adhesion alone can remain; and adhesion is promoted when one or more of the dimensions of the adhering bodies is small ($\alpha = T/T_m$). Relations (3) and (4) are, qualitatively at least, in accordance with such a picture, in that as l or r increases, the tendency to adhere should diminish.

The existence of a large temperature coefficient for k (see Table 1 and Fig. 2) indicates, however, that simple adhesion cannot represent the whole truth, for the temperature

TABLE 1.

T	592°	561°	534°	400°
k (Å hr.$^{-\frac{1}{2}}$)	24·0	20·0	11·0	5·0
Series	II	II	II	I

TABLE 2.

T	t (hr.)	S (m.^{2} g.$^{-1}$)	w (%)	MgO (%) (m)	A_{CO_2}	Density in CCl_4 (g. cm.$^{-3}$)	T	t (hr.)	S (m.^{2} g.$^{-1}$)	w (%)	A_{CO_2}	Density in CCl_4 (g. cm.$^{-3}$)
		Series I							Series II (*contd.*)			
400	0	56	30·93	0·0	—	—	561	18 *	67	1·4	35	3·46
	0·5	69	6·45	79·2	—	—		66	55	1·3	31	3·50
	1	151	2·94	90·5	—	—		330	34	1·1	23	3·55
	2	179	2·32	92·5	—	—						
	3	189	1·89	93·9	—	—	592	18 *	63	1·6	29	3·44
	12	190	1·79	94·2	—	—		66	47	1·4	24	3·48
	72	168	1·70	94·5	—	—		330	30	1·3	17	3·55
	356	107	1·42	95·4	—	—						
		Series II										
534	0 *	111	3·1	—	26	3·43						
	18	87	2·4		26·5	3·34						
	36	94, 68	2·3, 1·8		30, 27	3·44, 3·50						
	66	69	1·8		27	3·50						
	136	68	1·8		27	3·51						
	330	51	1·8		21	3·58						

* The material had been heated for 6 hours at 534° before the commencement of the experiment.
w = content of volatile matter. A_{CO_2} = area occupied per molecule of chemisorbed CO_2(Å^2).

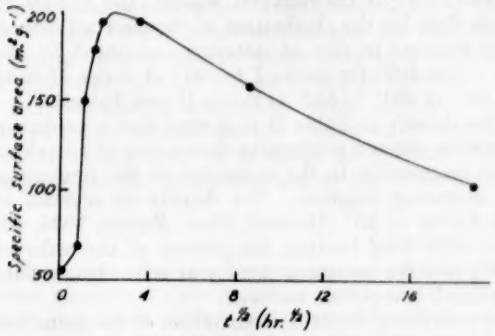
coefficient of k should then be of the order of the temperature coefficient of rigidity, and this is small; and, as will be shown shortly, it is quite likely that the rate of sintering is controlled by the rate of removal of a chemisorbed layer from the surfaces about to adhere, a process for which an energy of activation and therefore an appreciable temperature coefficient is to be expected.

The results of Series I, where the starting material was uncalcined magnesium hydroxide, may now be considered. In Fig. 3 the specific surface S has for convenience

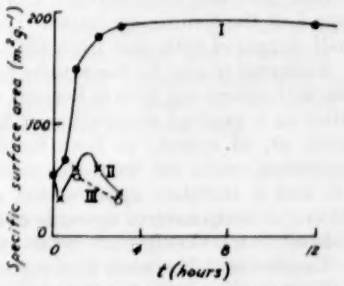
been plotted against $t^{\frac{1}{2}}$ for the experiment at 400°, and as is seen it first increases to a maximum and then slowly decreases. Comparison with the values of percentage decomposition m (calculated from the loss on ignition) given in Table 2 reveals that S is by no means proportional to m; thus whereas S increases only slightly whilst m increases from 0 to 79%, a further 10% decomposition sees the area increased by more than two-fold, and the next 2% conversion is accompanied by no less than 18% increase in area. Clearly, the production of new surface must result from some process which either occurs *after* the decomposition or at any rate proceeds more slowly than the decomposition; and a reasonable postulate is that the magnesium hydroxide decomposes to give the oxide in the form of a pseudo-lattice of the hydroxide, which later recrystallises to the stable form of the oxide (periclase). The recrystallisation would proceed from nuclei, each one giving rise to a micelle of oxide, the increase in specific surface being thus decided by the number of micelles present per original micelle of hydroxide (Gregg, Part I *loc. cit.*); the surface would be largely located on the walls of fine cracks produced by the shrinkage associated with the recrystallisation process. Once formed, the oxide would immediately sinter, probably by an adhesion mechanism as already

FIG. 3. FIG. 4.

Calcination of precipitated magnesium hydroxide.



At 400°.



I, 400°; II, 700°; III, 750°

indicated, the fine cracks giving place to a smaller number of wide cracks with a lower surface area.

In Fig. 4 the value of S is plotted against t for the early part of the experiment at 400° and for the whole of the experiments at 700° and 750°. The initial dip in the curve for 700° is probably real and due to the sintering of the unchanged magnesium hydroxide, the rise and subsequent fall being explained by activation and sintering just as before; the curve for 750° has two readings only, but there is little reason to doubt that its form would have been identical with that for 700° had more readings been taken in the first hour.

The data for content of volatile matter w are given in column 4 of Table 2. Since in the experiments of Series II the material had already been heated for 6 hours at 534° before commencing the experiment proper, it is clear that for comparable total times of heating w is consistently higher than in Series I at 400°—an unexpected result in view of the higher temperatures of Series II. The most likely explanation is that the whole, or most, of w in Series II represents combined carbon dioxide derived from the atmosphere during storage of the specimen, despite the use of a screw-topped bottle; and since w is (very roughly) proportional to the specific surface, a chemisorbed layer of carbonate on the surface is indicated. The values for the area A per molecule of carbon dioxide, calculated from S and w, are given in column 6. They are only approximate because of the difficulty of measuring w accurately, but are consistent with the reasonable assumption

that each chemisorbed molecule of carbon dioxide covers *three* ions of oxygen in the surface of the magnesium oxide, *i.e.*, two in addition to the one which is directly linked to the carbon atom; for the area occupied per molecule of carbon dioxide would thus be at least $3 \times 7{\cdot}8$ Å^2, *i.e.*, 23 Å^2—and perhaps somewhat greater for any isolated oxygen ion lying between neighbouring chemisorbed carbon dioxide molecules would have to remain vacant. According to this picture, when sintering occurs, chemisorbed carbon dioxide will be expelled from the surfaces as they adhere; and if this expulsion with its rather large energy of activation be assumed to control the overall rate of sintering, the high temperature coefficient already remarked on is qualitatively explained.

In the language of reaction kinetics it seems then that the " energy factor " controlling the rate of sintering may be determined by the expulsion of carbon dioxide, and the " frequency factor " by the micellar dimensions.

The volatile matter in Series I, for reasons already indicated, probably represents water only; and if the area per molecule is calculated (for the sintering branch of the curve for 400°, since bulk hydroxide may then be assumed absent), it comes to 32 Å^2 for 12 hr., 30 Å^2 for 32 hr. and 23 Å^2 for 23 hr. If one molecule of chemisorbed water is assumed to cover *two* oxygen ions in the surface of the solid, the proportion of surface covered with chemisorbed water is 0·49, 0·50, and 0·67 respectively. The results are too scanty to allow unequivocal conclusions to be drawn, but they do suggest that the sintering of Series I is accompanied by the elimination of chemisorbed water; the energy of activation for this process would be lower than for the elimination of chemisorbed carbon dioxide, and this may explain why the increase in rate of sintering (measured by the slope k of the " sintering branch "), *e.g.*, from 400° for Series I to 534° of Series II is so small compared with that from 534° to 561° or 561° to 592° in Series II (see Table 1).

Referring finally to the results for the density ρ (Table 2) it is seen that ρ gradually rises with increasing time of heating, denoting either a progressive destraining of a strained lattice or a gradual elimination of holes inaccessible to the molecules of the immersing liquid, or, of course, to both factors operating together. The density of crystals of magnesium oxide cut from the melt is 3·5761 at 25° (Durand, *Phys. Review*, 1936, **50**, 451) and it therefore appears that only after long heating, for periods of the order of 330 hr., at temperatures upwards of 530°, does the measured density of active magnesium oxide approach closely that of the unstrained, non-porous material.

Conclusion.—The work here reported provides a direct demonstration of the reduction of the specific surface of an active solid by the action of heat; and it shows that the extent of the reduction is increased by an increase in either the temperature or the time of heating. It also shows that " activation " of the solid need not coincide with the decomposition of the parent substance, but may follow it in time, being probably due to recrystallisation of a pseudo-lattice. The sintering is accompanied by an increase in apparent density and probably also by progressive elimination of chemisorbed water (or of chemisorbed carbon dioxide in older specimens) from the surface of the micelles.

The formulation in fully quantitative terms of a detailed mechanism for the sintering of active solids must, however, await further experimental and theoretical work.

Our thanks are offered to the University of London Research Fund for the loan of a galvanometer. One of us (K. H. W.) acknowledges receipt of a maintenance grant from the Further Education and Training Scheme, and another (R. K. P.) the receipt of a grant as student-in-training from the Department of Scientific and Industrial Research.

University College, Exeter. [*Received, July 21st*, 1954.]

The Production of Active Solids by Thermal Decomposition. Part VI. The Calcination of Magnesium Hydroxide.*

By S. J. Gregg and R. K. Packer.

[Reprint Order No. 5577.]

Two batches of magnesium hydroxide were precipitated, one almost ion-free and the other containing 1·22% of sulphate ion. Separate samples of each were then calcined for two hours at a succession of fixed temperatures, and a number of properties of the resultant active magnesium oxide were measured after cooling, including the specific surface area (S), the heat of immersion (H_L), and the density. The curves of specific surface and of heat of immersion against the temperature of calcination show a marked maximum corresponding to the chemical decomposition; the maximum is displaced towards higher temperatures, and its height is greater, for the sulphate-contaminated material. The rate of fall of S and of H_L with temperature of calcination is greater, denoting enhanced sintering, for this same material.

The production of active magnesium oxide by the thermal decomposition of magnesium hydroxide offers certain advantages for studying the preparation of active solids by thermal decomposition: magnesium hydroxide is a definite stoicheiometric compound, a *hydroxide*, and not a mere hydrated oxide of indefinite composition; and the product of decomposition, magnesium oxide, exists in one modification only and undergoes no polymorphic transformation. Moreover it can be deliberately contaminated with ions during preparation, or obtained nearly pure, thus permitting a study of the effect of impurity on the production and on the subsequent sintering of an active solid.

Experimental

Materials.—Two batches of magnesium hydroxide were prepared by precipitation, Batch *A* from magnesium chloride under conditions likely to minimise contamination, and Batch *B* from magnesium sulphate under conditions likely to favour adsorption of sulphate ions. Both precipitations were conducted in a closed aspirator *X* of 25 l. capacity fitted with an electrical stirrer entering through a mercury seal; two other aspirators *Y* and *Z* were fitted with delivery tubes drawn down at the end so as to form jets terminating near the bottom of *X*. The contents of *Y* and *Z* could thus be run into *X* at a rate controlled by screw-clips. All the distilled water used in making up solutions and in washing precipitates was boiled before use to expel carbon dioxide and stored in vessels protected by potassium hydroxide guard tubes. The outlet from *X* to the atmosphere was similarly guarded.

For Batch *A*, 10 l. each of N-magnesium chloride and of N-potassium hydroxide were run from the two aspirators *Y* and *Z* into *X*, which initially contained enough water to cover the jets; the precipitate was then allowed to settle, and after the supernatant liquor had been sucked off was washed repeatedly with distilled water (about 20 l. each time), and then with 0·025N-ammonia solution. There were twenty-eight washings in all, though even after the fifteenth a minute reaction for chloride ions was obtained. The sludge was then transferred to Winchester bottles and most of the water removed by warming in a water-bath at 65° and evacuation with a filter pump; the Winchesters were then cut open and the solid was dried (P_2O_5) in a vacuum desiccator, and stored in screw-topped bottles. The granular product was pure white and its chloride content—determined photometrically—was 0·015%, its loss in weight at 1000° being 30·93% [Calc. for $Mg(OH)_2$, 30·88%].

For Batch *B*, 10 l. of N-ammonia solution were added from aspirator *Y* to 10 l. of N-magnesium sulphate in *X*. The precipitate was washed as before, the last washings still giving a slight precipitate with barium chloride, and dried, also as before, to a more powdery product which, by analysis, contained 1·22% of sulphate ion. Its loss on ignition at 1000° was 31·83% [Calc. for $Mg(OH)_2$, if all the sulphate were lost as SO_3, 31·74%].

* Part V, preceding paper.

Procedure.—A "calcination series" was prepared from each batch by heating separate samples to each of a succession of fixed temperatures for 2 hr.: preliminary experiments on the open thermal balance (Gregg and Winsor, *Analyst*, 1945, **70**, 336) had shown that at 400° and 500° the rate of loss of weight became very small (though not zero) after 2 hr. The properties of the products were then examined as in Part V (*loc. cit.*), *viz.*, measurement of (1) sorption of oxygen and of nitrogen at 90·2° K and of nitrogen at 77·4° K; (2) sorption of carbon tetrachloride at 25° C; (3) the apparent density in carbon tetrachloride and in decalin; (4) the heat of immersion in carbon tetrachloride; (5) the loss on ignition (by raising to 980° on the thermal balance); (6) the sulphate content by gravimetric analysis, weighing as barium sulphate. The sorption isotherm of nitrogen at 77·4° K was also measured in some cases, by use of a low-temperature cryostat (cf. Tompkins and Young, *Trans. Faraday Soc.*, 1951, **47**, 77) with liquid oxygen, boiling under reduced pressure, as the refrigerant.

Results.—The isotherms of nitrogen, both at 90·2° K and 77·4° K, and of oxygen at 90·2° K were of Type II (B.E.T. classification) and the specific surface area S could be readily calculated from them by the usual B.E.T. procedure; the three values of S (cf. the table) corresponding to the three sets of isotherms agreed satisfactorily, usually within 10% or so and often better.

Temp. of calcination	Specific surface area * S_1	S_2	S_3	Density, ρ † 1	2	3	Content of volatile matter, w (%)	θ ‡	Pore volume v (cm.³ g.⁻¹)
Batch *A*									
15°	56	—	—	2·38	—	—	30·93	—	0·385
300	47	—	—	2·36	—	—	—	—	—
340	106	110	—	2·42	2·88	2·55	25·14	—	—
350	—	—	—	2·58	3·32	3·02	11·49	—	—
365	162	165	—	2·72	2·72	2·83	16·30	—	—
400	169	179	—	3·33	—	3·45	2·32	0·64	0·865
500	171	115	—	3·40	3·30	3·53	1·64	0·71	0·865
600	94	95	—	3·43	3·37	3·56	0·51	0·28	0·863
700	74	71	—	3·48	3·37	3·56	0·28	0·20	0·840
900	30	31	—	3·44	3·48	3·57	0	—	0·646
1400	—	—	—	3·47	2·88	—	0	—	0·007
Batch *B*									
15	32	33	34	2·36	—	2·39	31·83	—	0·057
365	40	38	38	2·91	—	3·06	10·53	—	0·059
400	118	123	129	3·31	—	3·43	2·93	—	0·155
425	—	196	—	3·37	—	3·46	2·04	—	—
450	—	209	197	3·42	—	3·51	1·14	—	—
500	166	171	185	3·45	—	3·55	0·46	—	0·226
600	75	84	80	3·45	—	3·56	0·29	—	0·169
700	—	38	—	3·47	—	3·57	0·15	—	—
900	9·3	11	11	3·46	—	—	0	—	0·015

* S_1, S_2, S_3 = specific surface area (m.² g.⁻¹) from sorption of oxygen at 90·2° K, of nitrogen at 90·2° K, and of oxygen at 77·4° K.

† 1, In CCl_4; 2, in decalin (cm.³ g.⁻¹); 3, calc. from w and true densities of MgO and of $Mg(OH)_2$ (cm.³ g.⁻¹).

‡ θ = fraction of surface covered with OH groups.

In Fig. 1 (*a*) the surface area (say S') has been calculated per gram of non-volatile material (MgO) from the values of S (say S_2) obtained with nitrogen at 90·2° K. The two quantities S_2 and S' are not in general identical because the content of volatile matter is usually appreciable; and the plot of S' against the temperature of calcination (Curves I and II) represents the change in the surface area of a given sample when heated for two hours at a given temperature if the effect of all previous heating could be ignored. Comparison with Curve III of Fig. 1 (*b*) which gives the percentage decomposition (calculated from the loss on ignition) as a function of temperature shows that with both batches there is a marked increase in area when water is expelled; but with the pure sample the increase is very marked whilst the decomposition is still far from complete, whereas with the sulphated sample there is much closer correspondence between the extent of decomposition and the increase in surface area. The relative increase in surface area from *B* to *C* is greater for the sulphated than for the pure material, being some five-fold as against some three-fold.

The values obtained for the percentage of sulphate for Batch *B* are: 15°, 1·76; 550°, 1·73; 600°, 1·54; 650°, 1·63; 900°, 1·35; the variation in sulphate content with temperature is

thus relatively and surprisingly small. The data for loss on ignition are given in the Table and for Batch *A* require little comment, for they clearly represent the " water " content of the samples; for Batch *B*, the values quoted contain an unknown contribution from the portion of sulphate volatilised at 980° and at the higher temperatures are particularly uncertain.

As will be noted, the sulphate content varies comparatively slightly with temperature and at 900° is still approximately three-quarters of its original value. It is interesting that the sulphate content of the unheated material is just sufficient to form a completed monolayer on the surface of the micelles if it be assumed that each sulphate ion covers an area of 30 Å², *i.e.*, four times that of an oxygen ion: the total area occupied by 1·76% of sulphate would then be 33 m.², exactly the specific surface area of the unheated material.

The data for density are also recorded in the Table, where they are compared with the density calculated for a mixture of magnesium oxide and magnesium hydroxide (true density 3·576 and 2·39 respectively) in proportions given by the water content. The experimental value is, at all temperatures and for both batches, distinctly below that calculated; even with 5 hours' heating at 1400° the measured density in carbon tetrachloride is some 3% lower than

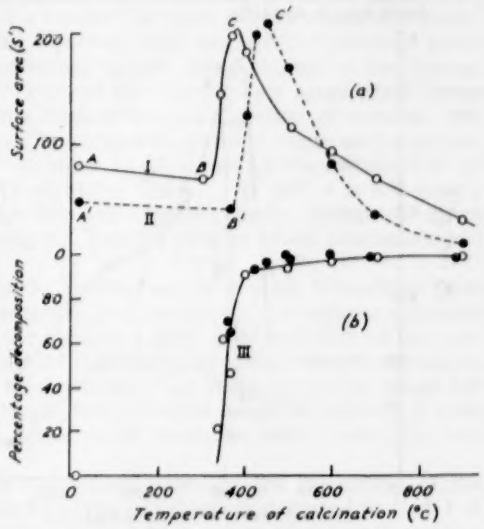


FIG. 1. *Calcination of magnesium hydroxide.*

(*a*) *Plot of S', the surface area in square metres per gram of non-volatile material, against the temperature of calcination; I, Batch* A *; II, Batch* B.

(*b*) *Plot of percentage decomposed against the temperature of calcination for both Batches* A *and* B. *Open circles, Batch* A *; solid circles, Batch* B.

the accepted figure for true density (3·576), determined on magnesium oxide crystals formed from the melt (Durand, *Phys. Review*, 1936, **50**, 451). In decalin the 1400° sample showed a density which is unaccountably low.

The heat of immersion H_L in carbon tetrachloride when plotted against the temperature of calcination (Fig. 2) gives a curve very similar in shape, for both batches, to that for specific surface area (Fig. 1); and the sorption isotherms of carbon tetrachloride are probably all of Type IV (B.E.T. classification), though in one or two instances it is difficult to decide between Type II and Type IV, owing to paucity of data near saturation. The data both for the isotherms and for the heat of immersion will be discussed in detail elsewhere.

From the carbon tetrachloride isotherms on Batch *A* and the oxygen isotherms on Batch *B* an approximate value of the pore volume of each sample has been calculated (by dividing the total number of grams adsorbed at the saturated vapour pressure by the ordinary liquid density at the temperature of the experiment). The values obtained (Table) differ strikingly for the two series, being at all temperatures up to and including 900° far smaller for the sulphated than for the pure material.

DISCUSSION

The results clearly demonstrate the effect of an ionic impurity on the curve representing activity as a function of temperature (cf. Fig. 1, curves I and II, and Fig. 2).

As explained in Part I, curves of this kind may be interpreted in terms of two opposing

effects: an *activation* due to the decrease in the size and an increase in the number of micelles consequent on a chemical decomposition, and a *sintering* of the product resulting in an increase in size and a decrease in the number of micelles. The sudden increase in the value of the area S' (BC and $B'C'$ of curves I and II, Fig. 1) corresponds to a sharp increase in the percentage decomposition m (curve III) but neither S' nor S is proportional to m, particularly with the pure batch. It is likely (cf. Part V) that the increase in the number of micelles is brought about by the recrystallisation—proceeding from nuclei—of the magnesium oxide from a pseudo-lattice of the hydroxide to the stable lattice, periclase; if there is an average of n nuclei per micelle of the "pseudo" oxide, the specific surface will increase n-fold.

From Fig. 1 it may be inferred that the presence of the sulphate ions affects the rate of recrystallisation rather than the rate of decomposition; for whereas the curves of

FIG. 2. *Plot of the heat of immersion H_I in carbon tetrachloride against the temperature of calcination; I, Batch A; II, Batch B.*

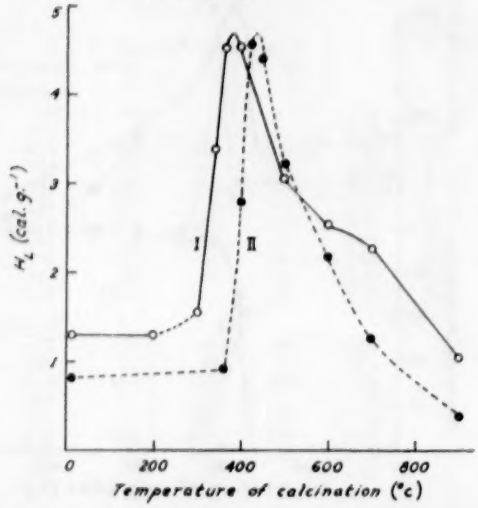
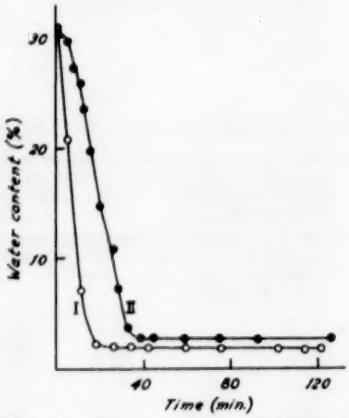


FIG. 3. *Isothermal decomposition of magnesium hydroxide (Batch A) on the thermal balance.*



Plot of water content against time: I, 500°; II, 400°.

percentage decomposition are very close to one another, the curve for specific surface area of the "sulphated" is considerably displaced from that for the "pure" batch, in the direction of higher temperature. This could be explained by the assumption that the rate of formation of nuclei follows a law of the form $dn/dt = Be^{-E/RT}$ and that both B and E are higher for the sulphated batch; for the higher E would mean that n and therefore the increase in S first become appreciable at higher temperatures for this batch, whilst the higher B would result in a proportionately higher maximum value for n and therefore for S. Data are too few and the system too complicated to permit B and E to be estimated quantitatively at present; nor is it possible to put forward a precise model for the effect of sulphate ions on these quantities, though one can see how the presence of such ions could distort the lattice in their neighbourhood in their own favour and so render more difficult the formation of nuclei of magnesium oxide.

From the fact that the curve for Batch B above 500° or so falls more sharply than that for Batch B, one infers that the presence of the sulphate ion promotes sintering; and a possible explanation suggests itself from a consideration of the pore volume (Table). That these are so low for the sulphated matèrial is probably due to the fact that this material was produced, in essence, by flocculation of a sol by sulphate ions; this process would tend to produce a compact precipitate of low pore volume in which micelles are

touching over relatively large areas, a condition which would tend to promote sintering. This picture is supported by the fact that the specific surface of the hydroxide of the sulphated batch before calcination was distinctly lower than that of the pure batch, where the flocculating effect would, of course, be less.

A second factor, which could operate alongside the first, is the surface diffusion of Mg^{2+} and SO_4^{2-} ions which would result in a filling-in of cracks and fissures (places of low adsorption potential to which mobile ions would tend to drift) and a consequent reduction in specific surface area. Such diffusion might perhaps be expected to become appreciable at temperatures near the Tammann temperature of bulk magnesium sulphate (*ca.* 430°), and could therefore be present over the whole of the " sintering " branch of curves I and II of Fig. 1 or of Fig. 2.

Attention should again be drawn to the extraordinary tenacity with which the last traces of " water " are held (cf. Gregg and Hill, *J.*, 1953, 3945; Gregg and Sing, *J. Phys. Coll. Chem.*, 1952, **56**, 1388; also Britton, Gregg, and Winsor, *J. Appl. Chem.*, 1952, **2**, 693, for traces of carbon dioxide in carbonates). It is difficult to believe that water, which is only released at temperatures of a hundred or more degrees above the decomposition temperature of the material, can represent bulk magnesium hydroxide which has eluded decomposition: the graphs of weight against time obtained on the thermal balance (Fig. 3) show that the " water " content falls sharply to a figure which varies only very slowly with time and points to a mode of combination distinct from the rest. It is reasonable to suppose that this " water " is present as hydroxyl groups on the surface, and assuming each " molecule of water " to cover 15 Å^2, values for the fraction θ of the surface covered with hydroxyl are readily calculated (Table). At 400° θ is not greatly below unity; it falls as the temperature rises, as expected, partly because of direct evaporation and partly because of sintering (cf. Part V), both of which processes would be accelerated by rise in temperature.

The fact that the experimental values for density are, in general, lower than those calculated, signifies the presence of lattice strain, or of an appreciable volume composed of holes too small to admit molecules of the immersing fluid, or of both factors together. That the second effect is relatively unimportant is indicated by the absence of appreciable drift in the density determinations, and of abnormally long times of equilibrium at low pressures in the carbon tetrachloride isotherms, both of which would be expected if holes were present of a size such that carbon tetrachloride molecules could enter only with difficulty.

Conclusion.—The formation of active magnesium oxide by the calcination of the hydroxide provides a clear example of the first type of behaviour described in Part I of this series in that the curve of specific surface against temperature of calcination shows a very definite maximum. The location of the maximum is affected appreciably, and the extent of sintering at any one temperature markedly, by the presence of sulphate ions in the original hydroxide precipitate.

Our thanks are offered to the London University Research Fund for the loan of a galvanometer, and to the Imperial Chemical Industries Research Fund for the loan of apparatus. One of us (R. K. P.) acknowledges receipt of a maintenance grant as a student-in-training from the Department of Scientific and Industrial Research.

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The Chemistry of Nitrosyl Complexes. Part I. Evidence for the Self-ionisation of Liquid Nitrosyl Chloride from Tracer Studies.

By J. Lewis and R. G. Wilkins.

[Reprint Order No. 5689.]

Complete exchange has been observed between tetramethyl- or tetraethyl-ammonium chloride (enriched with ^{36}Cl) and nitrosyl chloride within 10 minutes at $-5°$ or 3 minutes at $-36°$, respectively. The results are considered to favour a self-ionisation of the nitrosyl chloride rather than an ion-transfer process. The latter may occur in the other solvent systems examined by tracer methods. The exchange is not photochemical.

In connection with the investigation of certain addition compounds in nitrosyl chloride, we have studied the exchange of chloride ion, labelled with ^{36}Cl, with nitrosyl chloride. In many solvents a small amount of self-ionisation has been postulated to account for the reactions which occur in them. Isotopic exchange reactions have been used in an attempt to detect such ionisation since in a solvent system $X \rightleftharpoons Y^+ + Z^-$ the addition of either labelled Y^+ or labelled Z^- to the solvent should rapidly lead to labelling in X. In the case of nitrosyl chloride a self-ionisation $NOCl \rightleftharpoons NO^+ + Cl^-$ has been suggested by (Burg and Campbell, *J. Amer. Chem. Soc.*, 1948, **70**, 1964; Burg and McKenzie, *ibid.*, 1952, **74**, 3143) and hence rapid exchange between chloride ion and solvent would be expected. In our preliminary experiments (Lewis and Wilkins, *Chem. and Ind.*, 1954, 634) tetramethylammonium chloride was the soluble chloride but its limited solubility made exchange studies at temperatures lower than $-5°$ difficult. Tetraethylammonium chloride, which is much more soluble in nitrosyl chloride, could be used at $-36°$.

Experimental

Preparation of Tetramethylammonium Chloride containing ^{36}Cl.—Tetramethylammonium hydroxide (5 c.c.; 25% w/w solution) was treated with 3·12N-hydrochloric acid containing ^{36}Cl (0·48 μc/c.c. of solution; supplied by the Radiochemical Centre, Amersham) until a neutral solution was obtained (about 5 c.c.), and then evaporated. The solid chloride was dried in a vacuum for 12 hr. at 118° over phosphoric oxide (Found: Cl, 32·2. Calc. for $C_4H_{12}NCl$: Cl, 32·4%).

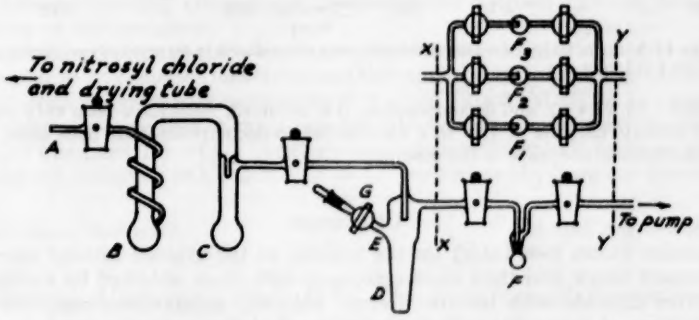
Preparation of Tetraethylammonium Chloride containing ^{36}Cl.—Hydrochloric acid containing ^{36}Cl (5 c.c. as above) was treated with tetraethylammonium hydroxide (about 8·7 c.c.; 25% w/w solution) until a neutral solution resulted and this was gently evaporated to dryness. The residue was recrystallised from acetone and the resulting needles were dried as above (Found: Cl, 21·3. Calc. for $C_8H_{20}NCl$: Cl, 21·4%). On one occasion a small amount of the crude active residue from the evaporation was recrystallised from ethylene dichloride (Vernon, Goldberg, and La Rochelle, *J. Amer. Chem. Soc.*, 1951, **73**, 2844) but the product was almost inactive and exchange must have taken place in the hot solvent.

Preparation of Nitrosyl Chloride.—Nitrogen dioxide (obtained by heating commercial lead nitrate in a metal bomb) was passed through a 2-ft. column of moist potassium chloride (Whittaker, Lundstrom, and Merz, *Ind. Eng. Chem.*, 1931, **23**, 1410), and the evolved nitrosyl chloride dried by passing through three 2-ft. columns of anhydrous calcium chloride. The gas was condensed to a deep-red liquid in a spiral worm (similar to *B* in the Figure) cooled in solid carbon dioxide–acetone.

Exchange Runs.—The apparatus (Figure) was thoroughly dried before an exchange run, being flamed under vacuum. Manipulations involving the tetraethylammonium chloride were carried out in a Tower's Manipulator Box. The spiral worm containing the liquid nitrosyl chloride was warmed and the middle fraction of evolved gas further dried by passing through a short length of calcium chloride, attached at *A*, and condensed in the bulb *B*. The nitrosyl chloride was again fractionally distilled and the middle fraction condensed in bulb *C*; this was fractionated into the exchange vessel *D*, up to a calibrated mark (about 5 c.c.). The procedure after this differed slightly depending upon which active chloride was used. (*a*) A known amount of tetramethylammonium chloride (about 18 mg.) was added to the nitrosyl chloride (about

−7°, just below the b. p.) by inverting a side-arm (not shown in the figure) attached at *E*. The liquid was vigorously stirred by manual magnetic stirring for about 5 min. during which the chloride dissolved; about one-third of the nitrosyl chloride was boiled off and condensed in one of the receivers *F*. The nitrosyl chloride solution was just prevented from boiling and after about 20 min. and then 60 min. the remaining nitrosyl chloride was removed and collected in the other receivers F_2 and F_3. (*b*) A known amount of tetraethylammonium chloride (about 50 mg.) packed in a small glass tube open at both ends was added through the vacuum-tap *G* to the nitrosyl chloride cooled in freezing ethylene dichloride (about −36°). The chloride was soon dissolved from the open tube and was stirred for 1—2 min. as described in (*a*). The nitrosyl chloride was removed at this temperature by applying a vacuum (vapour pressure of nitrosyl chloride at −36° = 170 mm., Burg and McKenzie, *loc. cit.*), it being possible to remove a fraction of nitrosyl chloride about 3 min. after the chloride had been added. Further fractions of nitrosyl chloride after about 10 and 30 min. were removed in the same way. In both (*a*) and (*b*), runs were carried out in the light and in the dark an dthe residue was analysed for chloride (Volhard; see below).

Counting Procedure.—Because of the relatively small amounts of activity involved after the necessarily large dilution of active chloride by inactive nitrosyl chloride, counting was done on solid samples where a higher efficiency of counting was obtained than with the more convenient counting in solution. The nitrosyl chloride was converted into a solid suitable for counting as follows: the nitrosyl chloride from *F* was almost completely solidified and added



to excess of sodium hydroxide solution, forming sodium chloride and sodium nitrite. The chloride was precipitated from the acidified (nitric acid) solution with silver or lead nitrate solution. The solid was washed with water, alcohol, and ether and dried at about 100° for 30 min. Most of the counting was done on silver chloride and although the results obtained were sufficiently accurate for our purposes, the silver chloride darkened on exposure to light and the activity changed by a small amount. In addition, the solid was usually crystalline, difficult to powder finely, and therefore not "matting" well by our methods. Lead chloride had none of these disadvantages and was used towards the end of the work. Matted samples were made on G.E.C. large flat planchets by a method very similar to that described by Popjak (*Biochem. J.*, 1950, **46**, 560) and by Adamson and Wilkins (*J. Amer. Chem. Soc.*, 1954, **76**, 3381). The amounts used were always the same and more than half of that required for "infinitely thick." The latter is about 190 mg./sq. cm. estimated from Feather's equation (see Taylor, "The Measurements of Radio Isotopes," Methuen, London, 1951, p. 71) and roughly confirmed experimentally. The variation of count with the amount of material was therefore very slight at the thicknesses used. Reproducibility was within 5%. Standard electronic equipment was employed for counting in conjunction with a G.E.C. mica end-window counter and a Panax Universal lead castle. Because of the low counts recorded, no resolving time correction was necessary (Taylor, *op. cit.*, p. 86). The usual allowance was made for background. The results are tabulated.

Stability of Organic Cationic Chlorides in Liquid Nitrosyl Chloride.—As found by Burg and McKenzie (*loc. cit.*), tetramethylammonium chloride was stable in boiling nitrosyl chloride. This was shown by analysing (for chloride; Volhard) the white residue remaining at the end of an exchange run after removal of the nitrosyl chloride under a vacuum (Found, for three experiments: Cl, 32·5, 32·35, 32·4. Calc. for $C_4H_{12}NCl$: Cl, 32·4%). Tetraethylammonium chloride

was also stable in contact with liquid nitrosyl chloride at −30°, but it was extremely difficult to remove all the nitrosyl chloride in a vacuum, even during several hours, and the residue was always very pale yellow. Nevertheless, the chloride content of the residue closely corresponded to that for the original compound (Found, for three experiments: Cl, 21·6, 21·65, 21·55. Calc. for $C_6H_{20}NCl$: Cl, 21·4%), and decomposition, if it occurred, must have been very slight. The removal of nitrosyl chloride at 100° in a vacuum led to decomposition of both salts, as shown by very low chloride contents of the residues.

Run no.	Inactive chloride NaCl (g.)	Inactive chloride NOCl (g.)	Active chloride Me_4NCl (mg.)	Active chloride Et_4NCl (mg.)	Dilution of chloride in NR_4Cl	Conditions	Time of contact (min.)	Activity of mixture (counts/min.)	Activity of of NOCl (counts/min.)
1	—	7·65	17·8	—	719	In light, −5°	10	—	92
							22	—	87
							57	—	86
2	—	7·84	17·7	—	741	In dark, −5°	10	—	80
							25	—	83
							60	—	81
	6·0	—	15·2	—	739	Mixed at room temp.	—	87	—
	6·0	—	32·8	—	342		—	174	—
3	—	7·68	—	50·6	445	In dark, −36°	3	—	106
				43·7			8	—	94
							50	—	101
	0·70	—	—	4·21	471	Mixed at room temp.	—	109	—
	0·70	—	—	6·31	314		—	150	—
4	—	7·68	—	6·50	299	In light, −36°	14	—	145
							31	—	138
	0·40	—	—	3·79	298	Mixed at room temp.	—	142	—

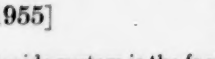
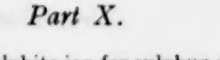
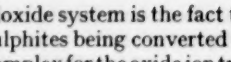
In runs 1—3, the activity of nitrosyl chloride was determined in terms of silver chloride, in run 4 in terms of lead chloride.

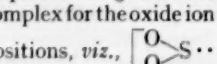
Discussion

The similar values (see Table) for the activity of the evolved nitrosyl chloride after various contact times, and their close agreement with those obtained by similar dilution of the active chloride with inactive sodium chloride, substantiate complete exchange within the time of separation. The method used almost certainly precludes exchange induced by the separation procedure. A photochemical path for exchange has been ruled out by work in the dark. Great care was taken to exclude moisture from the system to eliminate exchange paths involving water. These would probably be slow anyway as Burg and Campbell (*loc. cit.*) found that the reaction between water and nitrosyl chloride is slow at room temperature, and that the water can be recovered from the mixture.

Complete exchange, as evidence for self-ionisation in any solvent system, is complicated by the fact that usually an alternative path can account for the transfer of labelled atoms between solvent and solute. In the case of liquid ammonia, for example, the exchange of ammonium chloride containing ^{15}N with the solvent can be explained as well by a direct proton transfer, $^{15}NH_4^+ + NH_3 \rightleftharpoons {}^{15}NH_3 + NH_4^+$, as by ionisation of the ammonia. In addition, in liquid ammonia traces of water could interfere with the interpretation of the results, since water in a concentration of only 1 : 10^7 in liquid ammonia gives a detectable quantity of ammonium ions *via* the fast reaction $NH_3 + H_2O \rightleftharpoons NH_4^+ + OH^-$ (Ogg, *J. Chem. Phys.*, 1954, **22**, 560). Similar ambiguity will exist for other protonic solvents. In addition, the exact mode of ionisation of the solute must be known; the absence of exchange of thionyl compounds in liquid sulphur dioxide could arise from incomplete ionisation, *e.g.*, $SOCl_2 \rightleftharpoons SOCl^+ + Cl^-$, provided the ion $SOCl^+$ did not exchange with the solvent.

In the case of non-protonic solvents the alternative to a self-ionisation path for exchange involves transfer of a heavier particle, *e.g.*, an oxide ion in the cases of sulphur dioxide (cf. Johnson, Norris, and Huston, *J. Amer. Chem. Soc.*, 1951, **73**, 3052) and dinitrogen tetroxide, although this seems less probable than a proton transfer. Favouring this idea with the sulphur

dioxide system is the fact that there is an affinity of sulphite ion for sulphur dioxide, normal sulphites being converted by liquid sulphur dioxide into the metabisulphite. The activated complex for the oxide ion transfer reaction will have to contain the sulphur atoms in equivalent positions, *viz.*,  which is not the usual arrangement of this assortment of atoms in the metabisulphite ion, namely,  (Wells, "Structural Inorganic Chemistry," Oxford, 1950, p. 332). That this is not an insuperable difficulty, however, is shown by the fact that although there is a rapid exchange between nitric oxide and nitrogen dioxide enriched with ^{15}N (Liefer, *J. Chem. Phys.*, 1940, **8**, 301) and the activated complex must be (O–N · · · O · · · N–O), dinitrogen trioxide nevertheless has the unsymmetrical structure  (d'Or and Tarte, *Bull. Soc. roy. sci. Liége*, 1953, **22**, 276).

Interaction between NO^+ and NOCl is very likely in view of the acceptor and donor properties of these molecules. Solvation of the nitrosonium ion has been in fact established for the aluminium and ferric chloride addition compound (Burg and McKenzie, *loc. cit.*; Houtgraaf and De Roos, *Rec. Trav. chim.*, 1953, **72**, 963). The structure of the complex is  in which the nitrogen atoms are equivalent, and therefore complete exchange between labelled nitrosonium complexes and nitrosyl chloride would occur independently of self-ionisation.

Tetramethylammonium chloride has been shown by conductivity studies to dissolve in nitrosyl chloride to give chloride ions (Burg and McKenzie, *loc. cit.*). Exchange of the chloride ion *via* a nitrosonium ion transfer mechanism, $^{36}Cl^- + NOCl \rightleftharpoons NO^{36}Cl + Cl^-$, seems much less likely especially since ***both*** chloride ion and nitrosyl chloride are electron donors (see also Burg and Campbell, *loc. cit.*). The complete exchange observed is, however, in accordance with the self-ionisation $NOCl \rightleftharpoons NO^+ + Cl^-$ put forward by Burg and his co-workers (*locc. cit.*).

THE UNIVERSITY, SHEFFIELD. [*Received, August 30th*, 1954.]

The Senecio *Alkaloids. Part X.* The Structure of Rosmarinecine and its Synthesis from Retronecine.*

By L. J. DRY, M. J. KOEKEMOER, and F. L. WARREN.

[Reprint Order No. 5702.]

Rosmarinecine (I), proved to be a trihydroxy-compound by the formation of a tri-*O*-acetate (II) and trichloride (III), is dehydrated to anhydrorosmarinecine (VI). The hydroxyl group of anhydrorosmarinecine has been replaced by chlorine to give anhydrochloroplatynecine which is reduced to anhydroplatynecine (IX), which in turn is readily formed from platynecine and one mol. of toluene-*p*-sulphonyl chloride.

Retronecine (X) is oxidised by perbenzoic acid to epoxyretronecine *N*-oxide (XI) which is reduced catalytically with Raney nickel to rosmarinecine (I), and with platinum oxide to epoxyretronecine (XII) which in turn, with Raney nickel, gives rosmarinecine (I).

The reactions confirm the general structure previously advanced and permit a complete definition of the spatial configuration of the molecule.

ROSMARINECINE is a saturated tertiary amine for which structure (I) was proposed by Richardson and Warren (*J.*, 1943, 452). In advancing this structure the existence of a methylpyrrolizidine skeleton, characteristic of other *Senecio* alkaloids, was assumed. Furthermore, whereas experimental evidence did not exclude one alternative formula, structure (I) was preferred as it represented rosmarinecine as the hydroxyl derivative of platynecine (V), the dehydration of which would give retronecine.

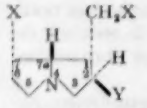
* Part IX, *J.*, 1952, 3445.

To test the validity of these assumptions additional experiments have been carried out. The existence of three hydroxyl groups was established by the acetylation of rosmarinecine to give tri-*O*-acetylrosmarinecine (II), characterised as its picrate, m. p. 138—139°, whilst the action of thionyl chloride gave a trichloro-compound (III). Benzoylation, however, gave only a dibenzoate (IV), the formulation of which follows from the work of Orechov and Konovalova (*Ber.*, 1936, **69**, 1908) who benzoylated the two hydroxyl groups of platynecine (V).

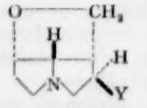
Orechov, Konovalova, and Tiedebel (*Ber.*, 1935, **68**, 1886) found that platynecine (V) and thionyl chloride gave anhydroplatynecine (IX) in high yield and only small quantities of the dichloro-derivative. Accordingly it appeared attractive to treat rosmarinecine (I) with this reagent to form the furan ring and replace the 2-hydroxyl group with chlorine to form anhydrochloroplatynecine (VIII). The reaction of rosmarinecine and thionyl chloride, however, resulted in the formation in good yield of a 2 : 7-dichloro-1-chloromethylpyrrolizidine, characterised as its picrate. This observation is more in accordance with the finding by Adams *et al.* (*loc. cit.*) that thionyl chloride and platynecine gave dichloromethylpyrrolizidine (I; but X = Cl, Y = H).

To establish that two of the hydroxyl groups were in an $\alpha\delta$-position to one another rosmarinecine was dehydrated with sulphuric acid to give anhydrorosmarinecine (VI), characterised as its picrate and containing one hydroxyl group since it yielded a monoacetyl derivative (VII), isolated as picrate, m. p. 190—192°. In the initial experiments the anhydro-compound was extracted from inorganic salt with chloroform in a Soxhlet apparatus; then in place of the base there slowly separated anhydrorosmarinecine dichloromethochloride, m. p. 198—200°. The anhydrorosmarinecine (VI) with thionyl chloride gave anhydrochloroplatynecine (VIII) which was reduced catalytically to anhydroplatynecine (IX), characterised as its picrate, m. p. 265—268° (decomp.) (cf. Orechov and Konovalova, *loc. cit.*).

Leonard and Felley (*J. Amer. Chem. Soc.*, 1950, **72**, 2537) placed the hydroxymethyl group of platynecine *trans* to the 7*a*-hydrogen atom in view of the ready dehydration to a furan ring. There was no evidence of the orientation of the 7-hydroxyl group because inversion during ring closure could not be excluded. We attempted to obtain information on the orientation of this hydroxyl group by the preparation of the toluene-*p*-sulphonyl ester of the primary hydroxyl group and the fission of this ester to form anhydroplatynecine; however, either there was no reaction or the product was anhydroplatynecine. The ready removal of toluene-*p*-sulphonic acid was indicative of the close proximity of the secondary hydroxyl group. This reaction occurs by the elimination of the sulphonate anion with the hydrogen ion from the 7-hydroxyl group and no inversion can occur. Thus the 7-hydroxyl group is *cis* to the 1-hydroxymethyl group and both are *trans* to the 7*a*-hydrogen atom.



(I) : X = Y = OH
(II) : X = Y = OAc
(III) : X = Y = Cl
(IV) : X = OBz, Y = OH
(V) : X = OH, Y = H



(VI) : Y = OH
(VII) : Y = OAc
(VIII) : Y = Cl
(IX) : Y = H

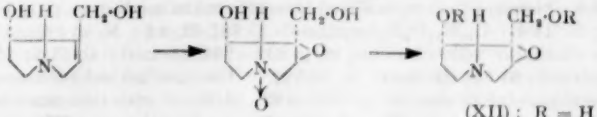
The N–$C_{(7a)}$ bond being assumed to be in the plane of the paper, the two rings are inclined towards each other behind the plane of the paper, thus:

An attempt was made to synthesise rosmarinecine (I) from retronecine (X) by way of the epoxide. Catalytic reduction of retronecine gave platynecine (V) (cf. Adams and Hamlin, *J. Amer. Chem. Soc.*, 1942, **64**, 2597) in which the hydrogen added to the outer fold of the pyrrolizidine nucleus, as was to be expected as the side above the plane of the paper is less structurally hindered. For the same reason it was expected that epoxyretronecine would have the β-configuration * (XII) and when opened by catalytic

* β refers to a bond projecting above the plane of the paper when the formula is oriented as shown in (I)—(IX).

reduction could give two products, one of which would be rosmarinecine (I). Since it was found here that rosmarinecine could not readily be directly dehydrated to senecionine (see following paper), it seemed likely that the 1-hydrogen atom, known to be β, and the hydroxyl group at $C_{(4)}$ were *cis* to each other, and that rosmarinecine therefore had a β-hydroxyl group at the latter position.

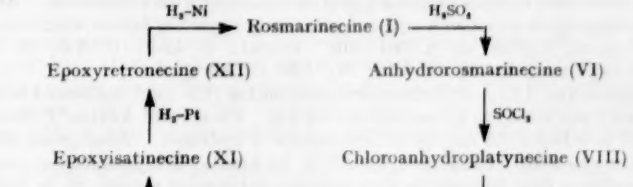
Retronecine readily reacted with perbenzoic acid to give isatinecine (retronecine *N*-oxide), which then slowly took up another atom of oxygen to give epoxyisatinecine. Isatinecine, however, could be epoxidised satisfactorily only in the presence of an initial excess of benzoic acid, a precaution unnecessary in the case of retronecine since the rapid formation of the *N*-oxide was accompanied by the generation of the required benzoic acid. The epoxyisatinecine was readily reduced with zinc dust (cf. Koekemoer and Warren, *J.*, 1951, 66), and catalytically in the presence of Adams platinic oxide, to give epoxyretronecine (XII) in quantitative yield. The epoxide was extremely stable to both



alkaline and acid hydrolysis. The compound (XII) was readily acetylated to a liquid diacetyl compound (XIII), isolated as picrate, m. p. 151—152°. Reduction of (XI) or (XII) with Raney nickel gave a semi-solid gum. The bulk of the product, which contained no glycol grouping (Criegee test, *Ber.*, 1931, **64**, 260), was rosmarinecine since it readily gave rosmarinecine picrate, m. p. 170°, triacetyl rosmarinecine picrate, m. p. 139°, and dibenzoyl rosmarinecine picrate, m. p. 179—180°.

The configuration of the hydroxyl groups assigned from the synthetic experiments is in agreement with our inability to obtain an *iso*propylidene ether with acetone.

Since the structures of retronecine (X), platynecine (V), and anhydroplatynecine (IX) are established (cf. Adams and Hamlin, *J. Amer. Chem. Soc.*, 1942, **64**, 2597; Adams and Leonard, *ibid.*, 1944, **66**, 257), that of rosmarinecine (I) previously advanced by Richardson and Warren (*loc. cit.*) is confirmed. Further these experiments indicate the similarity in the stereoconfiguration of the hydroxyl groups in platynecine and rosmarinecine as well as in retronecine.



Experimental

Some analyses are by Mrs. Y. Merchant of these laboratories.

Tri-O-*acetylrosmarinecine* (II).—Rosmarinecine (500 mg.) was refluxed with acetic anhydride (10 ml.), and the product poured into water and basified with sodium carbonate. The chloroform extract gave an oil which yielded with picric acid *tri*-O-*acetylrosmarinecine picrate*, monoclinic needles (from ethanol), m. p. 138—139·5° (Found: C, 45·6; H, 4·4; N, 10·7. $C_{20}H_{24}O_{12}N_4$ requires C, 45·5; H, 4·6; N, 10·6%).

Di-O-benzoylrosmarinecine (IV).—Rosmarinecine (3·1 g., 1 mol.) in pyridine (20 ml.) was treated at 0° with redistilled benzoyl chloride (5 ml., 2·4 mols.) dropwise. After 5 min. at 20° and 5 min. at 40° the dark red solution was poured on ice-water, treated with ammonia, and extracted with ether. The resulting solid from the ether extract, freed from pyridine in a vacuum and crystallised several times from 80% ethanol, gave the *dibenzoate*, m. p. 179—180° (Found: C, 69·1, 69·5; H, 6·1, 6·2. $C_{22}H_{23}O_5N$ requires C, 69·3; H, 6·1%), in quantitative yield.

Anhydrorosmarinecine (VI).—Rosmarinecine (2 g.) was added in portions to 70% sulphuric acid (15 ml.) at 0° and then heated at 100° for 2 hr. The cooled solution was poured into water, decolorised with charcoal, made alkaline with solid potassium hydroxide (30 g.), reacidified with dilute sulphuric acid, and evaporated under reduced pressure. The solid was ground with sodium carbonate and extracted (Soxhlet) with ethanol. The extract gave an oil which easily sublimed at 37°/6 μ to give anhydrorosmarinecine as colourless, very deliquescent prisms, m. p. 63—66° (Found: C, 59·4; H, 7·7; N, 8·9. Calc. for $C_8H_{13}O_2N$: C, 61·9; H, 8·4; N, 9·0%). This gave a *picrate*, which crystallised from ethanol in needles, m. p. 183—185° (Found: C, 43·7; H, 4·3; N, 14·4. $C_{14}H_{16}O_9N_4$ requires C, 43·75; H, 4·2; N, 14·6%). The *picrolonate* crystallised from ethanol in yellow laminæ, m. p. 232—234° (Found: C, 51·8; H, 5·2; N, 16·1. $C_{18}H_{21}O_7N_5$ requires C, 51·55; H, 5·05; N, 16·7%). The distilled anhydrorosmarinecine gave acetylanhydrorosmarinecine picrate, m. p. 190—192°, identical with that described below.

Extraction of the solid ground with sodium carbonate (see above) with chloroform resulted in the gradual separation of a solid from the chloroform extract. Recrystallisation of this product several times from methanol–acetone gave *anhydrorosmarinecine dichloromethochloride* as monoclinic prisms, m. p. 198—200° (decomp.) [Found: C, 39·2, 39·2; H, 5·7, 5·3; N, 4·9; Cl, 38·4; Cl (ionic) 16·4. $C_9H_{14}O_2NCl_3$ requires C, 39·4; H, 5·1; N, 5·1; Cl, 38·7; Cl (ionic) 12·9%].

The crude product (150 mg.) was acetylated as described for rosmarinecine. The oily product with picric acid gave O-*acetylanhydrorosmarinecine picrate* which crystallised from ethanol in birefringent needles, m. p. 190—192° (Found: C, 45·1; H, 4·1; N, 13·2. $C_{16}H_{18}O_{10}N_4$ requires C, 45·1; H, 4·3; N, 13·1%). *Anhydrorosmarinecine hydrochloride* crystallised from ethanol–acetone as prismatic needles, m. p. 173—176° [Found: C, 50·3; H, 7·5; N, 7·2; Cl (ionic), 17·6. $C_8H_{14}O_2NCl$ requires C, 50·1; H, 7·4; N, 7·3; Cl, 18·5%].

Anhydrochloroplatynecine (VIII).—Anhydrorosmarinecine (400 mg.) was treated at 0° with redistilled thionyl chloride, a copious evolution of hydrogen chloride occurring. After 6 hours' heating under reflux the excess of reagent was removed under reduced pressure. The sticky residue was treated with cold water. The solution, extracted with chloroform to remove resins, was made alkaline with sodium carbonate and re-extracted with chloroform. An oily product from the chloroform gave with picric acid *anhydrochloroplatynecine picrate* which crystallised from ethanol in prismatic needles, m. p. 204—208° (Found: C, 42·0; H, 3·5; N, 14·4; Cl, 8·9. $C_{14}H_{15}O_8N_4Cl$ requires C, 41·75; H, 3·75; N, 13·9; Cl, 8·8%).

Anhydroplatynecine (IX).—Anhydrochloroplatynecine (130 mg.), recovered from the picrate, in ethanol (5 ml.) was added to Raney nickel (500 mg.; Covert and Adkins, *J. Amer. Chem. Soc.*, 1 32, **54**, 4117) in ethanol (25 ml.) in an atmosphere of hydrogen. Absorption of hydrogen was complete in 3 hr. (19·8 ml. Calc. for $C_8H_{12}ONCl$: 18·3 ml.). The product was an oil, the picrate of which crystallised from ethanol to give anhydroplatynecine picrate, m. p. and mixed m. p. 264—268° (Found: C, 46·0; H, 4·4; N, 15·2. Calc. for $C_{14}H_{16}O_8N_4$: C, 45·6; H, 4·4; N, 15·2%).

Trichloride (III) *from Rosmarinecine*.—Rosmarinecine (750 mg.) was treated with freshly distilled thionyl chloride (5 ml.) at 0° and then heated for 3 hr. on a water-bath. The product, worked up as described above, gave an oil which gave a *picrate*, m. p. 194—196° (Found: C, 36·7; H, 3·2; N, 13·7; Cl, 22·65. $C_{14}H_{15}O_7N_4Cl_3$ requires C, 36·7; H, 3·3; N, 12·2; Cl, 23·0%).

Epoxyisatinecine (XI).—(*a*) Isatinecine (4·5 g., 1 mol.) in chloroform (135 ml.) containing benzoic acid (6 g.) was added dropwise at −10° to a stirred solution of perbenzoic acid (7 g., 1·9 mols.) in chloroform (110 ml.) and kept at −6° for 8 days; oxidation was then complete. The solution was extracted with 2N-hydrochloric acid (100 ml.); the aqueous extract was washed with chloroform, made alkaline with sodium carbonate, and evaporated to dryness under reduced pressure. Extraction of the powdered residue with boiling ethanol (150 ml.) gave the *epoxide* as a white solid (4·3 g.) which crystallised from methanol as monoclinic prisms, decomp. 200°, $[\alpha]_D^{21}$ −40·5° (*c*, 1·2 in H_2O) (Found: C, 51·5; H, 7·2; N, 7·65. $C_8H_{13}O_4N$ requires C, 51·3; H, 7·0; N, 7·6%).

(*b*) Retronecine, treated similarly with perbenzoic acid, absorbed 1 atom of oxygen in

30 min. to give isatinecine, and 2 atoms after 140 hr. to give epoxyisatinecine identical with the above.

Epoxyretronecine (XII).—(*a*) Epoxyisatinecine was reduced with zinc dust and hydrochloric acid, and the product worked up as described for the reduction of platynecine *N*-oxide (Koekemoer and Warren, *loc. cit.*). The product crystallised from ethanol–acetone, to give *epoxyretronecine* as prismatic needles, m. p. 172—173°, $[\alpha]_D^{22}$ −40·9° (*c*, 0·95 in H_2O) (Found: C, 55·9; H, 7·7; N, 8·0. $C_8H_{13}O_3N$ requires C, 56·2; H, 7·7; N, 8·2%). (*b*) Epoxyisatinecine, reduced with hydrogen in the presence of Adams catalyst, gave epoxyretronecine (Found: C, 56·1; H, 7·5; N, 7·9%).

Di-O-*acetylepoxyretronecine* (XIII).—Epoxyretronecine was refluxed with acetic anhydride and the oily product, treated with picric acid, gave *di*-O-*acetylepoxyretronecine picrate* which crystallised from ethanol in yellow needles, m. p. 151—152° (Found: C, 44·8; H, 4·2; N, 11·3. $C_{18}H_{20}O_{12}N_4$ requires C, 44·6; H, 4·2; N, 11·6%).

Reduction of Epoxyisatinecine.—Epoxyisatinecine (1·25 g.) in absolute ethanol (100 ml.) with Raney nickel (2 g.) absorbed hydrogen (301 ml. at N.T.P., *i.e.*, 1·7 mols.) in 2 hr. The product was partly solid and gave a crystalline *picrate*, m. p. 169—170° after recrystallisation from ethanol, undepressed by rosmarinecine picrate, m. p. 170° (Found: C, 42·1; H, 4·7; N, 14·3. $C_{14}H_{16}O_{10}N_4$ requires C, 41·8; H, 4·5; N, 13·9%). The *metho-Reineckate* was readily purified from aqueous acetone (Found: C, 31·1; H, 4·8; N, 19·2; S, 25·4. $C_{13}H_{24}O_9N_7S_4Cr$ requires C, 30·8; H, 4·8; N, 19·4; S, 25·3%). The picrate of the acetylated product, m. p. 139°, and the benzoyl derivative, m. p. 179—180°, likewise showed no m. p. depression when mixed with triacetylrosmarinecine picrate and dibenzoylrosmarinecine respectively.

Reduction of epoxyretronecine by this method gave a gum which yielded derivatives identical with those above.

The authors acknowledge a bursary (to M. J. K.) and grants from the South African Council for Scientific and Industrial Research, with respect to this and the following paper.

Department of Chemistry and Chemical Technology,
University of Natal, Pietermaritzburg, S. Africa. [*Received, September 6th*, 1954.]

The Senecio *Alkaloids. Part XI.* The Conversion of Rosmarinine into Senecionine and the General Structure of the* Senecio *Alkaloids.*

By M. J. Koekemoer and F. L. Warren.

[Reprint Order No. 5703.]

Rosmarinine (III) readily gives a monotoluene-*p*-sulphonate (V) which on hydrolysis gives senecic acid and *epi*rosmarinecine. Refluxing (V) with pyridine causes elimination of toluene-*p*-sulphonic acid with the formation of senecionine. The action of thionyl chloride on (III) gives anhydrorosmarinine in which water is seemingly eliminated from the acid moiety.

In Part X * it was shown that rosmarinecine was hydroxyplatynecine and could be prepared by the hydration of retronecine by way of its epoxide. Leisegang and Warren (*J.*, 1949, 486) assigned the complete structure for retrorsine (I); and with the general structure of the acids (cf. Kropman and Warren, *J.*, 1950, 700) and bases in mind, it seemed reasonable to assume that the acids were similarly orientated in the other *Senecio* alkaloids, *e.g.*, senecionine (II), rosmarinine (III), and platyphylline (IV). This assumption received some confirmation from the observation that the trihydroxy-base rosmarinecine (cf. Part X) formed only a dibenzoyl derivative as does the dihydroxy-base platynecine. This would indicate an analogous esterification of platyphylline and rosmarinine.

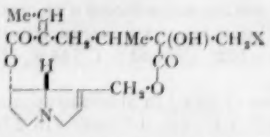
To test this concept attempts were made to dehydrate rosmarinine. Use of thionyl chloride gave anhydrorosmarinine (picrate, m. p. 243—246°), which gave rosmarinecine on hydrolysis, together with, probably, anhydrosenecic acid (3-methylhepta-2 : 5-diene-2 : 5-dicarboxylic acid).

Rosmarinine (III) readily gave the toluene-*p*-sulphonate ester (V). This readily gave senecic acid on hydrolysis; but the basic fission product after acetylation gave a picrate,

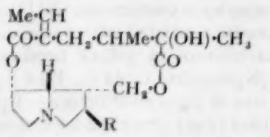
* Part X, preceding paper.

m. p. 143—144°, which was different from triacetylrosmarinecine picrate, m. p. 139—140° as well as from diacetylretronecine picrate, m. p. 143—144°. It is seemingly *epi*-rosmarinecine which would be expected from the inversion during the hydrolysis of the toluene-*p*-sulphonyl group.

Rosmarinine toluene-*p*-sulphonate in refluxing dry pyridine lost toluene-*p*-sulphonic acid, to yield the expected senecionine, m. p. 234—236°, which was characterised by identification of retronecine and senecic acid on hydrolysis as well as by comparison with an authentic specimen.



(I): X = OH. Retrorsine (β-longilobine)
(II): X = H. Senecionine



(III): R = OH. Rosmarinine
(IV): R = H. Platyphylline
(V): R = *p*-Me·C_6H_4·SO_3

An authentic specimen of senecionine was prepared from *Senecio squalidus* (cf. Barger, *J.*, 1936, 742; Koekemoer and Warren, *J.*, 1951, 66), collected in May in North London. The plant contained 0·025% of senecionine and 0·037% of senecionine *N*-oxide, showing that our previous conclusion with regard to the occurrence of the *Senecio* alkaloids also as *N*-oxides was applicable to senecionine and to *Senecio* species growing in temperate climates.

Apart from the formation and reduction of the alkaloid *N*-oxides, the preparation of senecionine from rosmarinine is the first example of the conversion of one complete *Senecio* alkaloid into another. These results establish the structure of senecionine (II), rosmarinine (III), and platyphylline (IV). The structure of integerrimine, shown by Kropman and Warren (*J.*, 1950, 700) to be the *trans*-form of senecionine, follows, so that the structures of five *Senecio* alkaloids are now established. All occur in the plant also as their *N*-oxides (cf. Koekemoer and Warren, *loc. cit.*).

The structures advanced for the different alkaloids reveal a close similarity (cf. earlier Parts of this series). The structures of the other *Senecio* alkaloids will doubtless conform to the same general carbon skeleton.

Experimental

*Formation of Toluene-*p*-sulphonate Ester of Rosmarinine.*—Rosmarinine (2 g., 1 mol.) in redistilled dry pyridine (15 ml.) at 0° was added to toluene-*p*-sulphonyl chloride (2·2 g., 2 mol.) in cold pyridine (10 ml.) at such a rate that the temperature did not exceed 0°. After 72 hr. at 4° the slightly reddish solution was poured into cold 5N-ammonia (75 ml.) and extracted with ether. The extract was washed with a little water, dried (Na_2SO_4), and evaporated, to yield a white solid (2·5 g.), m. p. 114—118°. After complete removal of pyridine in a vacuum-desiccator the solid was crystallised five times from 50% ethanol to yield the *ester* as needles, m. p. 120° (Found: C, 58·8; H, 6·2; N, 2·5; S, 6·3. $C_{25}H_{33}O_8NS$ requires C, 59·1; H, 6·55; N, 2·8; S, 6·3%). Chloroform extraction failed to yield unchanged starting material.

*Hydrolysis of Rosmarinine Toluene-*p*-sulphonate.*—The sulphonate (1·5 g., 1 mol.), suspended in water (50 ml.), was heated with hydrated barium hydroxide (3 g.) at 100° for 2 hr., cooled and made acid to Congo-red with 2N-hydrochloric acid (7·5 ml.). Extraction with ether (5 × 40 ml.) yielded after washing, drying, etc., 0·42 g. of crude solid, which after recrystallisation from ethyl acetate had m. p. 145—147° alone or mixed with senecic acid. The acid solution remaining was basified with solid barium hydroxide and evaporated to dryness under reduced pressure. Extraction of the powdered dry residue with boiling chloroform yielded 100 mg. of hygroscopic, somewhat discoloured, base which, after acetylation, yielded an oil whose *picrate*, m. p. 143—144°, on admixture with triacetylrosmarinecine picrate, m. p. 139—140°, and diacetylretronecine picrate, m. p. 143—144°, respectively, gave large m. p. depressions (Found: C, 45·5; H, 4·2; N, 11·2. $C_{20}H_{24}O_{13}N_4$ requires C, 45·5; H, 4·6; N, 10·6%).

*Senecionine from Rosmarinine Toluene-*p*-sulphonate.*—The toluene-*p*-sulphonate (400 mg.) was refluxed for 3 hr. with dry pyridine (7 ml.), cooled, poured into 5N-aqueous ammonia

(50 ml.), and extracted with ether. The ether solution gave a small amount of crystalline material, m. p. 230—232°. Extraction with chloroform yielded more material of the same m. p. The combined solid residues (180 mg.), contaminated with a little gummy material, were washed with cold acetone and recrystallised twice from ethanol to yield senecionine as monoclinic prisms, m. p. 234—236° undepressed on admixture with senecionine from *Senecio squalidus* (Found : C, 64·4, 64·4; H, 7·2, 7·6; N, 4·1, 4·3. Calc. for $C_{18}H_{25}O_5N$: C, 64·5; H, 7·5; N, 4·2%). Hydrolysis of this senecionine gave senecic acid, m. p. 145—147°, and retronecine, identified as diacetylretronecine picrate, m. p. 143—144°.

Senecionine from S. squalidus.—The dried and ground *S. squalidus* (1 kg.) collected in May in North London was extracted as described by Koekemoer and Warren (*J.*, 1951, 66). The extraction gave senecionine (0·25 g.) directly and an additional quantity (0·37 g.) after reduction.

Anhydrorosmarinine.—Rosmarinine (2 g.) was treated at 0° with freshly distilled thionyl chloride (8 ml.) and then heated for 3 hr. under reflux. Excess of reagent was removed under reduced pressure, and the residue treated with cold dilute hydrochloric acid and freed from resins by extraction with chloroform. The solution was basified with sodium carbonate and extracted with chloroform; this extract gave an oil which solidified in a vacuum. This solid which was readily soluble in most organic solvents gave with picric acid, and after several crystallisations from ethanol, *anhydrorosmarinine picrate* as yellow needles, m. p. 243—246° (Found : C, 51·05; H, 4·9; N, 9·5. $C_{24}H_{28}O_{12}N_4$ requires C, 51·05; H, 5·0; N, 9·9%).

The anhydrorosmarinine (1·5 g.) was refluxed with sodium methoxide, prepared from sodium (1 g.), for 6 hr. The solution was acidified with hydrochloric acid and evaporated to dryness in a vacuum. The solid was ground with sodium carbonate and extracted (Soxhlet) with acetone to yield rosmarinecine.

Department of Chemistry and Chemical Technology,
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The Senecio *Alkaloids. Part XII.* The Synthesis of* (±)-erythro-3-*Hydroxy*-2-*methoxy*-4-*methylpentane*-3-*carboxylic Acid.*

By Leonard J. Dry and Frank L. Warren.

[Reprint Order No. 5704.]

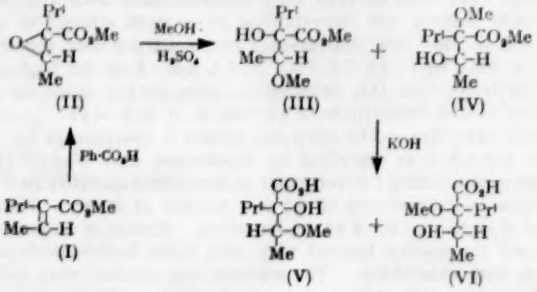
Methyl 4-methylpent-2-ene-3-carboxylate (I) is oxidised with perbenzoic acid and the epoxide (II) subjected to acid methanolysis to yield, after saponification, (±)-*erythro*-3-hydroxy-2-methoxy-4-methylpentane-3-carboxylic acid (V).

Heliotrinic acid, m. p. 93—95°, $[\alpha]_D$ −12°, has been obtained by the hydrolysis of heliotrine (Menshikov, *Ber.*, 1932, **65**, 974) and *iso*heliotrine (Trautner and Neufeld, *Austral. J. Sci.*, 1949, **11**, 211) and was shown to be 3-hydroxy-2-methoxy-4-methylpentane-3-carboxylic acid (Menshikov, *J. Gen. Chem. U.S.S.R.*, 1939, **9**, 1851). Adams and van Duuren (*J. Amer. Chem. Soc.*, 1953, **75**, 4636) reported that on demethylation it yielded an acid, m. p. 89°, which showed no m. p. depression with trachelantic acid which we had shown was (+)-*threo*-2 : 3-dihydroxy-4-methylpentane-3-carboxylic acid, m. p. 92° (*J.*, 1952, 3445). We have synthesised (±)-*erythro*-3-hydroxy-2-methoxy-4-methylpentane-3-carboxylic acid (V), which we had expected to yield heliotrinic acid.

4-Methylpent-2-ene-3-carboxylic acid (see Dry and Warren, 1952, *loc. cit.*) was esterified by way of the acid chloride without isomerisation since the ester (I) yielded the original acid on hydrolysis. The ester with perbenzoic acid readily gave methyl 2 : 3-epoxy-4-methylpentane-3-carboxylate (II). In boiling methanolic sulphuric acid this yielded, after hydrolysis, an acid mixture which was shown, by quantitative oxidation with lead tetra-acetate (Leisegang and Warren, *J.*, 1950, 702), to contain about 80% of an α-hydroxy-acid (V). That a certain amount of the 2-hydroxy-ester (IV) should be formed during acid methanolysis follows from the reasoning applied to the acid methanolysis of methyl αβ-epoxybutyrate (Dry and Warren, *J. S. African Chem. Inst.*, 1953, **6**, 14), where the α-hydroxy-isomer was obtained in 77% yield. The *erythro*-configurations of (V) and (VI)

* Part XI, preceding paper.

follow from the *trans*-addition of methanol to the epoxide (II) (Dry and Warren, 1953, *loc. cit.*) with inversions at positions 2 and 3 respectively.



The mixture (V) + (VI) was obtained as an oil even after purification and prolonged desiccation. The acid (V) was readily separated by crystallising the morphine salts from water or acetone, the hydrated salt, m. p. 187—189°, of the racemic acid (V) being obtained. The salt yielded an oily, optically inactive α-hydroxy-acid which was not investigated further. The anhydrous morphine salt, m. p. 208—209°, of (V) was obtained from ethanol–ether and gave an α-hydroxy-acid which gradually crystallised. The acid, m. p. about 40°, characterised as the *p*-bromophenacyl ester, m. p. 138°, showed no rotation, was very hygroscopic, and appeared unlikely to be the racemic form of heliotrinic acid. Demethylation gave a product, m. p. 149°, showing no m. p. depression with (±)-*erythro*-2 : 3-dihydroxy-4-methylpentane-3-carboxylic acid, m. p. 150° (Dry and Warren, 1952, *loc. cit.*). Since the optically active form of this acid does not racemise under the conditions of demethylation, resolution of (V) had apparently not occurred and could not be achieved by fractional crystallisation of the morphine salts.

Experimental

Methyl 4-*Methylpent*-2-*ene*-3-*carboxylate*.—4-Methylpent-2-ene-3-carboxylic acid (30 g.) in ether (50 ml.) was refluxed for 90 min. with thionyl chloride (21 ml.), the ether evaporated, the residual liquid treated with methanol (20 ml.) at 0°, and the whole heated to 100°. The product (24 g.), b. p. 79—83°/45 mm., was redistilled to give *methyl* 4-*methylpent*-2-*ene*-3-*carboxylate* (23 g.), b. p. 74°/36 mm. (Found : C, 67·8; H, 9·9. $C_8H_{14}O_2$ requires C, 67·6; H, 9·9%). With boiling alcoholic potassium hydroxide it yielded immediately the pure acid, m. p. and mixed m. p. 54°.

Methyl (±)-2 : 3-*Epoxy*-4-*methylpentane*-3-*carboxylate*.—Methyl 4-methylpent-2-ene-3-carboxylate (21·4 g., 1·0 mol.) in dry N-chloroformic perbenzoic acid (400 ml., 1·3 mols.) was set aside for 15 days at 6—8°; oxidation was then complete. The solution was extracted with 2N-sodium hydroxide (180 ml.), washed with dilute hydrochloric acid and 10% aqueous sodium chloride, dried ($MgSO_4$), and distilled, to yield the (±)-*epoxy-ester* (20·5 g., 0·86 mol.), b. p. 98—99·5°/35 mm. (Found : C, 61·2; H, 8·8. $C_8H_{14}O_3$ requires C, 60·7; H, 8·9%).

(±)-erythro-3-*Hydroxy*-2-*methoxy*-4-*methylpentane*-3-*carboxylic Acid*.—The foregoing ester (17·8 g.), sulphuric acid (2·2 ml.), and methanol (60 ml.) were refluxed for 3 hr., anhydrous sodium acetate (8 g.) was added, the excess of methanol evaporated under reduced pressure, and the product worked up as above. The ester mixture (15 g.), b. p. 112—115°/31 mm., was hydrolysed by boiling potassium hydroxide (18 g.) in 70% ethanol (200 ml.) for 1 hr. The acid product, freed from a small quantity of unchanged ester, was extracted with chloroform and worked up in the usual way, all solvent being evaporated under reduced pressure, to give an oily acid mixture (11·1 g.) Found : equiv., 183; CO_2, 14·8 ml. at N.T.P. Calc. for $C_8H_{16}O_4$: equiv., 176; 17·8 ml. for 1 mol. of CO_2). It gave a barium salt (Found : OMe, 12·5. Calc. for $C_8H_{15}O_4Ba_{0·5}$: OMe, 12·7%).

The acid mixture (8·1 g., 1 mol.) in 50% ethanol (200 ml.) was warmed with morphine (1 mol.), and the solution evaporated under reduded pressure to 100 ml. and cooled to 0°. Large prisms (10 g.), m. p. 180—184°, separated. Evaporation of the mother-liquor to 40 ml. and cooling to 0° yielded a further crop (8·7 g.) of the same salt, m. p. 180—182°. After three

recrystallisations from water a *salt* (2·5 g.), m. p. 187—189°, not raised on further recrystallisation, was obtained (Found : C, 62·2; H, 7·7; OMe, 6·5. $C_{35}H_{35}O_7N,H_2O$ requires C, 62·6; H, 7·8; OMe, 6·5%). The salt (2·4 g.) yielded an oily acid, $[\alpha]_D$ ±0° (*c*, 1 in H_2O), which did not solidify after sublimation at 70°/0·1 mm. The same salt was obtained by recrystallisation from acetone, boiling out with small quantities of acetone, and by crystallising an aqueous solution containing equal parts of the sodium and the morphine salt. When twice recrystallised from ethanol–ether, however, a *salt*, m. p. 208—209°, was obtained (Found : C, 64·6; H, 8·0; OMe, 6·6. $C_{35}H_{35}O_7N$ requires C, 65·0; H, 7·6; OMe, 6·7%). The latter reverted to the former, m. p. 187—189°, on recrystallisation from water, and yielded a very hygroscopic acid, m. p. *ca.* 40°, $[\alpha]_D$ ±0° (*c*, 1 in H_2O), crystallising in needles after 4 months in a desiccator and giving an intense yellow colour with ferric chloride. The *p-bromophenacyl ester*, m. p. 138°, crystallised from aqueous alcohol in stout prisms (Found : C, 51·9; H, 6·0; Br, 21·7; OMe, 8·2. $C_{16}H_{21}O_6Br$ requires C, 51·5; H, 5·7; Br, 21·4; OMe, 8·3%).

Demethylation. The methoxy-acid (30 mg.) was heated at 100° with 48% hydrobromic acid (5 ml.) for 2 hr., and the solution diluted somewhat and extracted with ether. The washed and dried ether extracts were evaporated and the residue sublimed at 90°/0·5 mm.

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Studies in Hydrogen-bond Formation. Part II. The Use of Refractive-index Measurements to Detect Intermolecular Complex Formation in Solution.*

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(*With an Appendix.* By JOHN C. EATON.)

[Reprint Order No. 4469.]

The square of the refractive index may be used equally as well as the dielectric constant (see Part I *) for detecting the ratio in which organic molecules associate intermolecularly in binary solution, with the added advantage that aqueous as well as non-aqueous solutions can be studied. In particular, hydrogen-bond complexes can be detected by this means, and typical results are given. Anion–cation association is also detectable, but no firm evidence has been obtained of the detection of other forms of association. The method appears equally useful for detecting strong or weak complexes. The reality of the existence of many compounds so detected has been demonstrated by a variety of procedures, including molecular-weight determination, preparation of solid complexes, and comparison with complexes previously reported, either by preparation in substance or detection by infra-red spectrophotometry. The method is rapid and simple, it requires only small quantities of substances (solutions at least as dilute as 0·01M have been used successfully), and it appears to have some advantages over hitherto-used procedures. It can be employed to detect intra- as well as inter-molecular bonds.

PART I * described preliminary experiments upon the use of dielectric-constant measurements to detect intermolecular hydrogen-bonding between pairs of organic solutes in non-aqueous solutions. Plots of dielectric constant against molar ratio of the solutes (at constant total molarity) were shown to be linear, changes of slope occurring at ratios which were interpreted as corresponding to the composition of intermolecular complexes.

* Part I, *J.*, 1952, 2799.

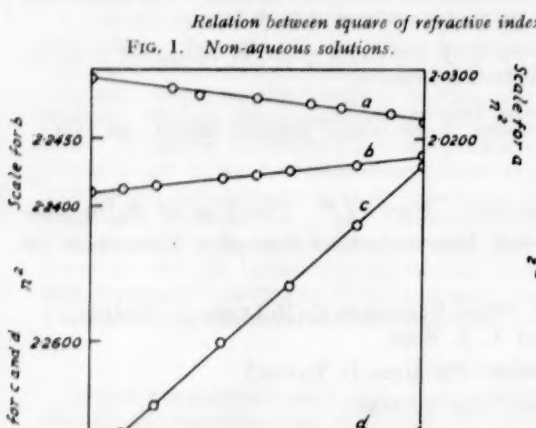
In Part I, p. 3800, last line of the second paragraph, *for* " hydrogen " *read* " carbon "; p. 3802, formula (III), lower line, *for* " $C_5H_5{\cdot}OH)=N{\cdot}C_4H_9$ " *read* " $C_5H_5{\cdot}C(OH)=N{\cdot}C_4H_9$."

The present paper describes an alternative method of detecting complex formation which may be used with both non-aqueous and aqueous solutions. The results obtained by the two methods are compared and a detailed examination is described of the validity of their interpretation as evidence of the presence of hydrogen-bond complexes.

Use of Refractive-index Measurements.—It was desired to work with aqueous solutions, and the dielectric-constant method used in Part I being unsuitable for this purpose, consideration was given to the measurement of some other physical constant. The refractive index appeared to fulfil the criterion of ready determination to a high degree of precision with small amounts of materials. By Maxwell's law, the square of the refractive index of a substance is equal to its dielectric constant, and therefore this parameter should, like the dielectric constant, vary linearly with the concentration of a solution. Since refractive index and dielectric constant cannot be measured at the same field frequency, and because anomalous dispersion occurs in dipolar substances, Maxwell's law is not generally

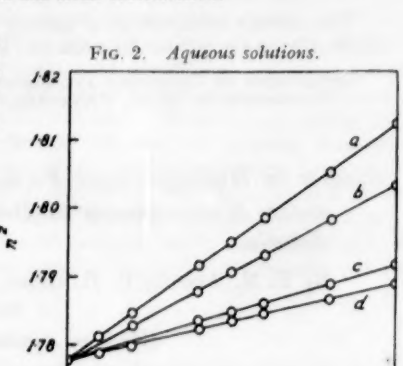
Relation between square of refractive index and molar concentration.

FIG. 1. *Non-aqueous solutions.*



a, Water in dioxan (20°).
b, Phenol in toluene (19°).
c, Azobenzene in toluene (19°).
d, Benzoquinone in toluene (19°).

FIG. 2. *Aqueous solutions.*



a, Glucose or mannitol (19°).
b, Phenol (19°).
c, Glycerol (20°).
d, Dimethylformamide (19°).

obeyed. It was therefore necessary to examine empirically the relationship between the square of the refractive index and the concentration of non-aqueous and aqueous solutions over the limited range of concentrations proposed to be employed. The results of this examination are summarised in Figs. 1 and 2, which show that the relationship is quite linear * for a variety of typical compounds in both non-aqueous and aqueous solutions up to at least double the maximum concentration (0·25M) used in the present work.

This test was then followed by one for additivity. Fig. 3 shows that the square of refractive index is truly additive for binary solutions, of constant molarity, of azobenzene and benzoquinone, two substances not capable of hydrogen-bond interaction. When, however, substances which are capable of interaction are examined, *viz.*, azobenzene and phenol (Fig. 7), the curve is virtually linear, but shows two slope changes, corresponding to intermolecular complexes of 1 : 1 and 1 : 2 ratio, as detected also by the dielectric-constant method (Part I, Fig. 2). An examination of some 33 different non-aqueous binary solutions, of which details will be given in later papers, then revealed that the changes in

* When the change in n is very small it is of course unnecessary to plot n^2, for n itself then varies linearly with concentration.

slope observed occur at the same respective ratios whether measurement is made by dielectric-constant or refractive-index methods. Further, it was found that aqueous solutions give the same type of curves as do non-aqueous solutions when examined by the latter method, changes in slope occurring at molar ratios which correspond in many cases to the occurrence of an expected hydrogen-bond complex.

Previous Work.—Apparently, refractive-index determinations have not hitherto been used thus, but Pushin and Matavulj (*Z. physikal. Chem.*, 1932, *A*, **158**, 290; *A*, **161**, 341; *A*, **162**, 415; 1933, *A*, **164**, 80), Pushin and Rikovski (*ibid.*, 1932, *A*, **161**, 336), Pushin, Matavulj, Rikovski, and Nenadović (*Bull. Soc. chim. Belgrade*, 1940—1946, **11**, 72; through *Chem. Abs.*, 1948, **42**, 2167), and Pushin, Matavulj and Rikovski (*ibid.*, 1948, **13**, 38, 165, 173; through *Chem. Abs.*, 1951, **45**, 6475; 1952, **46**, 2894), using binary ***mixtures*** of certain organic liquids, plotted refractive index, f. p., etc., directly against molar composition. They observed many examples of systematic variation from arithmetic mean values, and obtained curves showing maxima corresponding in many cases to intermolecular complex formation. They detected, *e.g.*, complexes of piperidine with phenols; of acetic acid with certain primary, secondary, and tertiary amines (in several cases corresponding to known solid complexes; *e.g.*, equimolar complexes with phenylhydrazine, piperidine, pyridine, or quinoline); of aniline (1 mol.) with phenol or *o*-chlorophenol (1 mol.) or acetic acid (2 mols.); of formic acid (2 mols.) with aniline, mono- or di-methylaniline, pyridine or

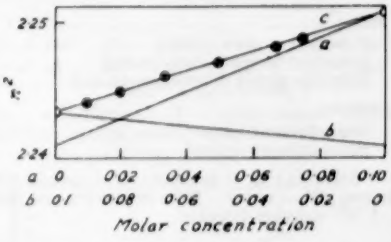


FIG. 3. *Additivity of square of refractive index for non-interacting solutes in toluene.*

a, Azobenzene.
b, Benzoquinone.
c, Binary solution.

quinoline (1 mol.); of benzylamine (1 mol.) with thymol (probably 1 mol.); and undefined complexes of quinol with *o*- and *p*-chlorophenol, cresols, guaiacol, or thymol; no complexes were detected between aniline and *p*-chlorophenol, cresols, or guaiacol. Evidence of molecular association of a second component mixed with benzene or toluene was obtained in some cases.

Confirmation of Complex Formation by Other Methods.—There were thus good grounds for believing that either of the present methods gives valid evidence of the presence of intermolecular complexes, but it was nevertheless considered that confirmation of this belief by as many other independent methods as possible would be desirable. Accordingly, a variety of procedures has been adopted in order to check the validity of the method. These include: (*a*) comparison with the composition of known solid complexes; (*b*) molecular-weight determinations; (*c*) comparison with infra-red spectrophotometric data; (*d*) examination of compounds known to contain chelate bonds; (*e*) comparison with certain interactions in monolayers; (*f*) a further study of the theoretical basis of the curves obtained; (*g*) examination of the consistency of the results and their relation to the known association properties of various compounds used. These results are now discussed.

(a) *Solid complexes.* In Table 1 a number of solid complexes between various organic compounds and alcohols or phenols, described by Pfeiffer ("Organische Molekülverbindungen," Stuttgart, F. Enke, 2nd edn., 1932), are shown, in comparison with identical or closely similar complexes detected in solution by the present methods. Fig. 4 shows evidence given by refractive-index measurements confirmatory of the existence of one of these complexes (benzoquinone + quinol, 1 : 1) in (dioxan) solution.

The same type of complex will not necessarily exist both in the crystalline state and in solution, and in fact a number of examples in Table 1 show that the solvent itself may

prevent interaction. (This point will be considered more fully in a later paper.) Nevertheless, there is good agreement between the data from the different sources.

It was hoped that this information could be supplemented by examination of solid complexes prepared from the solutions used in the present work. Only four such solutions have actually been found satisfactorily to deposit solid complexes, *viz.*, ether (or toluene)

TABLE 1. *Intermolecular complexes of hydroxylic compounds.*

Components	Molar ratio: As solid (Pfeiffer)	Molar ratio: In solution * (present work)
Aldehydes and ketones		
Acetaldehyde–ethanol	1 : 1	1 : 1 (W)
Benzaldehyde–ethanol	—	1 : 1 (W)
Acetone–methanol	—	1 : 2 (C) (D)
Acetone–phenol	1 : 2	† (E, W)
Di*iso*butyl ketone–phenol	—	1 : 2 (D)
Amine		
Aniline–phenol	1 : 1	1 : 1; (1 : 2); † (W) (T)
Carboxylic acids		
Acetic acid–phenol	—	1 : 1 (T)
Benzoic acid–phenol	—	1 : 1 (T)
Trichloroacetic acid–phenol	1 : 1	1 : 1 (T)
Esters		
Dimethyl oxalate–phenol	1 : 2; 1 : 4	1 : 2 (D)
Dimethyl terephthalate–phenol	—	1 : 4 (T)
Ethylene glycol dibenzoate–phenol	—	1 : 4 (T)
Quinone		
Benzoquinone–phenol	1 : 2	2 : 1; 1 : 2 (T)
Benzoquinone–quinol	1 : 1	1 : 1 (D)

* Solvents: B = benzene; C = carbon tetrachloride; D = dioxan; E = diethyl ether; T = toluene; W = water. Data in parentheses denote uncertain indications.
† No complex detected.

solutions of diethylamine with *p*-nitrophenol and resorcinol respectively. Analyses of these complexes when previously prepared (see Part I) did not exactly correspond to an integral ratio of the components. The discrepancies were attributed to possible selective solution of one component by the solvent used for washing. The preparations have now been repeated with suitable precautions and the elementary analyses now correspond with integral ratios of components (1 : 2 in both cases), though it is admittedly not easy to formulate the structure of such complexes. On account of precipitation, refractive-index measurements cannot be carried out with solutions in the same solvent as used for the preparations, but by using dioxan as a solvent, in which the complexes are quite soluble, no precipitation occurs and curves can be obtained (Fig. 5) which show changes of slope corresponding to the analyses of the solids; the change in the diethylamine–*p*-nitrophenol curve is slight, but definite, that in the diethylamine–resorcinol curve at the 2 : 1-ratio is only just discernible,* but there is a clear indication of a 1 : 1-complex, not obtained in solid form. Solutions in water give evidence of complexes of different integral ratios.

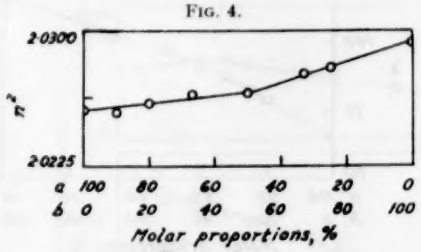
(b) *Molecular-weight determination.* Four pairs of compounds were selected for examination by the f. p. method in benzene. One of these, azobenzene–phenol, was chosen because, when examined by both the present methods (see above) it appears to form two distinct complexes of different ratio; the other three, because they appear to form unusual complexes perhaps by the less common mechanism of bonding through hydrogen attached to carbon. This will be discussed later. From data plotted on the basis shown (Figs. 7—10), *viz.*, apparent molecular weight of combined solute against molar ratio, the presence of an intermolecular complex should normally be demonstrated by a maximum in the curve at the appropriate ratio(s). In fact, all the expected

* *Added in Proof.*—This change in the curve has now been confirmed by use of a refractometer of higher precision.

discontinuities are evident, though in three of the five instances they are only just so. In two systems (Figs. 8 and 10) minima are obtained, *i.e.*, complex formation *lowers* the apparent molecular weight. Low molecular-weight values can be attributed to solvation of solute by solvent (cf. Skau and Wakeham in " Physical Methods of Organic Chemistry," Vol. I, ed. Weissberger, New York, Interscience Publishers, Inc., 1945, Chap. I; see also Chipalkatti, Giles, and Vallance, *J.*, 1954, 4375). The azobenzene–phenol system is clearly complicated by association of the phenol itself and the curve is difficult to interpret. Even

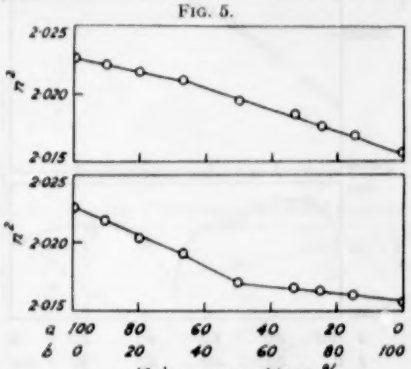
Relation between square of refractive index and component ratio in binary solutions in dioxan.

FIG. 4.



a, Benzoquinone.
b, Quinol.

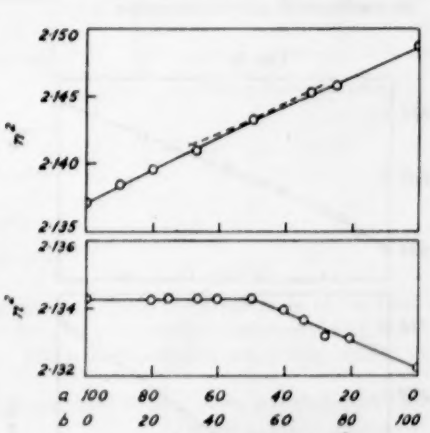
FIG. 5.



Top: *a*, *p*-Nitrophenol; *b*, diethylamine (20°).
Bottom: *a*, Resorcinol; *b*, diethylamine (20°).

FIG. 6.

Top: *a*, Benzyl alcohol; *b*, Azobenzene (0·1M) at 20°.
Bottom: *a*, Dimethylformamide; *b*, Phenol (0·05M) at 16°.
Solvent: Carbon tetrachloride.

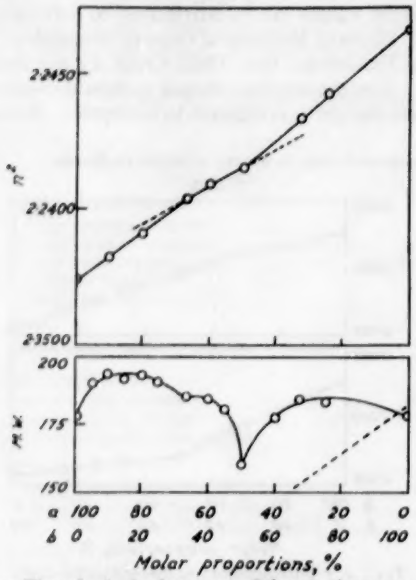


so, the discontinuities are above the theoretical line for no combination. The high intermediate sections of the curve must represent separation of complex on freezing, which can in fact be observed owing to the colour of azobenzene. Whatever the detailed interpretation of the discontinuities in these curves may be, they and the corresponding dielectric-constant or refractive-index plots agree in showing that at certain simple integral molar ratios of the solutes, some physical change occurs in the properties of the solutions.

In addition, Pushin and Matavulj (*loc. cit.*) confirmed the molar ratios of complexes detected in binary liquid mixtures, by f. p. determinations, and Laurent (*Compt. rend.*, 1935, **201**, 554) obtained a solid complex of phenol and aniline with a molar ratio (2 : 1) the same

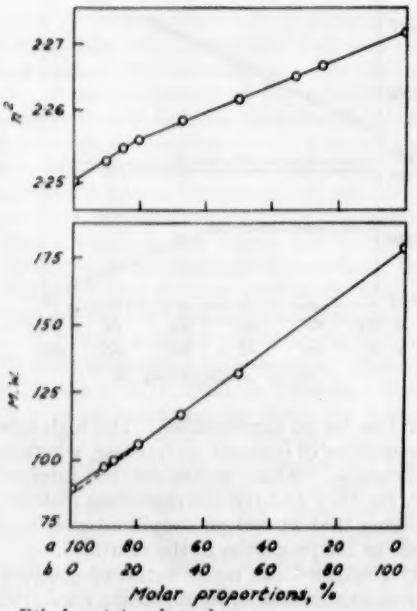
Relation between molar ratio, square of refractive index, and apparent molecular weight in binary solutions

FIG. 7.



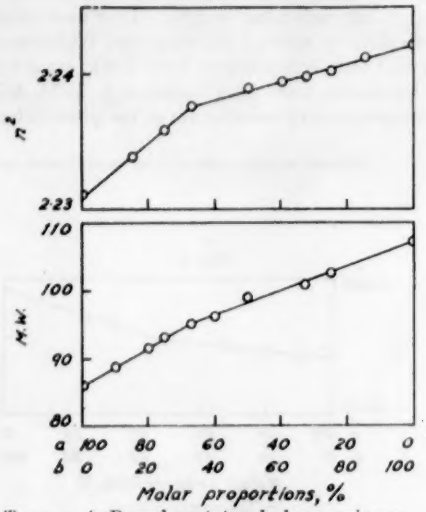
a, Phenol; *b*, Azobenzene. Solvent: benzene. Broken line in lower graph is theoretical plot for no combination and no association.

FIG. 8.



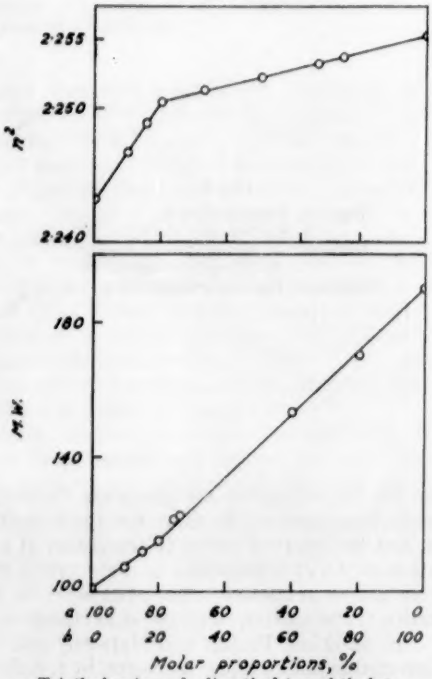
a, Ethyl acetate; *b*, azobenzene.
Solvents: Top, toluene (17°); bottom, benzene.

FIG. 9.



Top: *a*, *iso*Propyl acetate; *b*, benzoquinone.
Solvent: toluene.
Bottom: *a*, Ethyl acetate; *b*, benzoquinone.
Solvent: benzene.

FIG. 10.

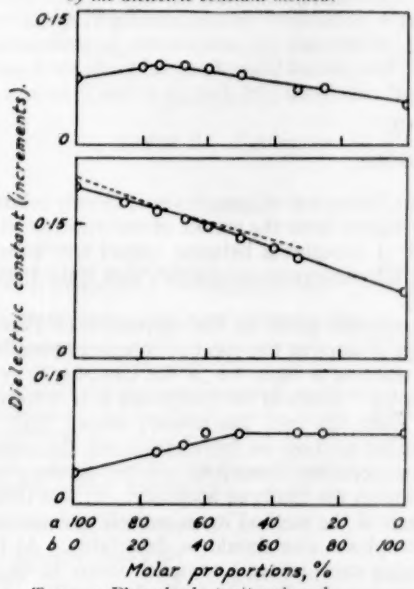


a, Triethylamine; *b*, dimethyl terephthalate.
Solvents: Top, toluene; bottom, benzene.

as found by dielectric-constant measurements on binary solutions, and also confirmed by cryoscopic measurements.

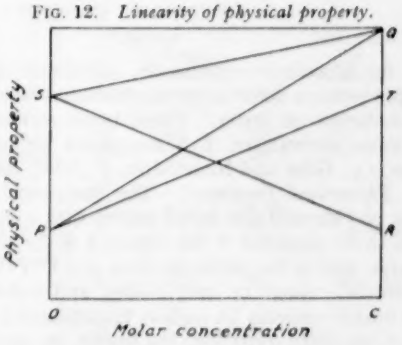
(c) *Infra-red spectrophotometry.* Flett (*J. Soc. Dyers Col.*, 1952, **68**, 59) and Tsuboi (*Bull. Chem. Soc. Japan*, 1952, **25**, 60) have given thermodynamic data for hydrogen-bond formation between pairs of aromatic compounds in carbon tetrachloride solutions, obtained by infra-red spectrophotometry. They determined heats, etc., of reaction by the method of measuring the change in height of an absorption band with change in temperature. This does not actually give an unequivocal measure of the ratio of components in the complex, but the ratio can usually be estimated, at least if the number of participating

FIG. 11. *Detection of intramolecular bonding by the dielectric constant method.*



Top: *a*, Phenol; *b*, *p*-nitrophenol.
Middle: *a*, Phenol; *b*, nitrobenzene.
Bottom: *a*, Phenol; *b*, *o*-nitrophenol.

FIG. 12. *Linearity of physical property.*



molecules is not more than about three or four, from the magnitude of the heat changes. In Table 2 some of Flett's and Tsuboi's data for compounds most resembling those we have examined are compared with our own. The systems studied are closely similar and in two

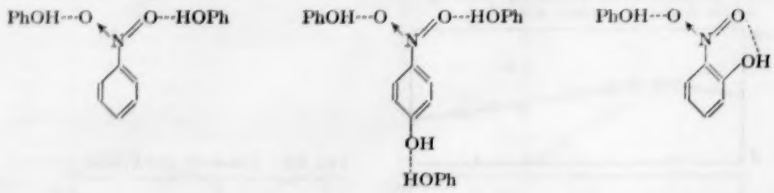
TABLE 2. *Comparison of present results with those of infra-red spectrophotometry.*

Complex between	Molar ratio and solvent *		
	Flett †	Tsuboi †	Present method
Anisole, benzyl alcohol	1 : 1	—	—
Anisole, phenol	—	—	1 : 1 (B)
Benzaldehyde, phenol	—	1 : 1	1 : 1 (W)
Benzyl acetate, phenol	1 : 1	—	—
*iso*Propyl acetate, phenol	—	—	1 : 1 (T)
Dimethylformamide, diethylamine	—	—	1 : 1 (B)
Dimethylformamide, diphenylamine	1 : 1	—	—
Dimethylformamide, phenol	1 : 1	—	1 : 1 (B; C; D; W)
Azobenzene, benzyl alcohol	1 : 1	—	1 : 1 (C)
Nitrobenzene, phenol	—	1 : 1	1 : 2 (B)

* Solvents: B = benzene; C = carbon tetrachloride; D = dioxan; T = toluene; W = water.
† Both these workers used carbon tetrachloride as solvent, and the ratios are assumed.

examples (cf. Fig. 6) are in fact identical. In all cases the two methods give parallel results.

(d) *Chelated compounds.* If true complex formation is shown by these methods, then the masking of the reactivities of pairs of individual groups in a molecule by chelation should be capable of demonstration thereby, since it will lead to a corresponding reduction in the number of possible intermolecular bonds. This has been tested and found to apply in a number of cases, which will be discussed in detail in a subsequent paper (see also Table 3), but a particular example may be quoted here, *viz.*, the evidence that phenol forms with nitrobenzene, *p*-nitrophenol, and *o*-nitrophenol, 2 : 1, 3 : 1, and 1 : 1 complexes, respectively (Fig. 11), which may be formulated as below



(e) *Monolayer experiments.* Evidence of the formation of complexes of closely related types to some detected in this work has been obtained from the results of experiments with monolayers on water. These types include 1 : 1 complexes between quinol and benzoquinone derivatives, 2 : 1 complexes between *o*-hydroxyazo-compounds and quinol, etc. (see, *e.g.*, Giles and Neustädter, *J.*, 1952, 3806).

Theoretical Treatment.—The theoretical treatment given in the Appendix of Part I (*loc. cit.*) showed that linear curves with a change of slope at the point of complex formation are to be expected if the value of K for the reaction is high, *i.e.*, if the complex is very stable, and in the particular case of a 1 : 1 complex. Many of the complexes now detected, however, cannot be very stable, and indeed Flett (*loc. cit.*) has already shown that, in 12 binary systems (in carbon tetrachloride) similar to those we have examined, the values of K are often quite low, the lowest, at room temperature, being 3·82, yet the curves given by this method are always apparently linear, within the limits of accuracy. It was therefore necessary to re-examine the theoretical basis of the method in an entirely general way with a view to determine whether unstable complexes also should be detectable. At the same time the opportunity was taken to examine cases where a complex occurs having a ratio other than 1 : 1, or where more than one complex is present simultaneously. The full treatment is given in the Appendix. It is there shown that the graph of the physical constant used against solute molar ratio can be expressed simply in terms of a deviation $z(S_{XY} - S_X - S_Y)$, where z is the number of molecules of complex X_mY_n formed, and S_{XY}, etc., are the slopes of the curves for the constants of the respective individual components of the solution. The graph of z against the number of molecules of X present consists of two straight lines, intersecting at the point corresponding to the composition of the complex, only if $K = \infty$, but for all values of K the graph has a single maximum at this same point. This will give a maximum or a minimum in the curves as plotted in this work, according as the value of $(S_{XY} - S_X - S_Y)$ is positive or negative. Thus in the special circumstance where $S_{XY} = S_X + S_Y$, *i.e.*, where the physical constant of the complex is the additive value of those of its components, no deviation at all should occur. This has been experienced in practice, as mentioned below, but it appears to take place only at one temperature, and at temperatures above and below this deviations are observed. The graphs for all the systems studied are thus strictly not linear, but it will be seen from the figures that the deviations from linearity are barely discernible.

The argument may be extended to cases in which two compounds, X and Y, combine to form more than one complex, *e.g.*, XY and X_2Y. Here there are two equilibria co-existing in the solution :

$$X + Y = XY \text{ and } XY + X = X_2Y$$

and the concentrations of the reactants will adjust themselves so that the equilibrium constants in the mixture are the same as in the separate systems. The curve can therefore be divided into halves, at least to a first approximation, one of which, between $X = Y$ and $X = 0$, has no change of slope, and the other, between $X = Y$ and $Y = 0$, has one corresponding to X_2Y, there being also a change at the intersection of the halves. A similar treatment may, in fact, be applied to conditions where more than two complexes can be formed, and in the present work as many as three have sometimes been detected in the same solution.

Relation of Results to Known Properties of Typical Solutes.—A series of compounds was selected for test to determine whether pairs of simple hydrogen-bonding substances would be found to have the expected complex ratios by this method, and in fact Table 3, (ii) and (iii), shows that they did (cf. also Part I, Table 1); and also to determine whether other forms of intermolecular association would be discernible in the curves, particularly (*a*) anion–cation association, (*b*) association between aromatic nuclei in planar molecules arising from short-range physical forces, and (*c*) various types of dipole–dipole interaction. The results [Table 3 (i), (iv), (v)] show that (i) is certainly detectable, but the series of tests

TABLE 3. *Typical results of refractive-index measurements.*

Solutes		Solution			Mol. ratio of complex
a	*b*	Solvent *	Total mol. concn.	Temp.	(*a* : *b*)
(i) *Acids and bases*					
Sulphanilic acid → *β*-naphthol	Glycine	W	0·1	19°	1 : 1
Aniline → 2-naphthol-3 : 6-disulphonic acid	Triethylamine	W	0·05	20	1 : 2
(ii) *Phenol–phenol and phenol–quinone pairs*					
Quinol	Phenol	W	0·25	19, 35	1 : 2
,,	Benzoquinone	D	0·1	20	1 : 1 (Fig. 4)
(iii) *Phenol with chelated, unchelated, and isomeric compounds*					
Nitrobenzene	Phenol	B	0·25	18	1 : 2 (Fig. 11)
o-Nitrophenol	,,	—	,,	,,	1 : 1 ,,
p-Nitrophenol	,,	—	,,	,,	1 : 3 ,,
Aniline → 2-naphthol-3 : 6-disulphonic acid	,,	W	0·05	20	1 : 1 —
Sulphanilic acid → 1-naphthol	,,	,,	0·25	20	1 : 1; 1 : 2; 1 : 3
Sulphanilic acid → 2-naphthol	,,	,,	,,	18	1 : 1
(iv) *Electron-donor pairs*					
Acetone	Benzoquinone	C	0·05	20	†
,,	Azobenzene	D	0·1	18	†
Pyridine	,,	C	0·05	17	†
,,	Triethylamine	C	0·1	20	†
Benzoquinone	Azobenzene	T	0·1	19	† (Fig. 3)
,,	Diisobutyl ketone	C	0·05	20	†
Aniline → 2-naphthol	Pyridine	B	0·25	20	†
(v) *Pairs with hydrocarbons*					
Benzene	Ethylene dichloride	C	0·05	20	†
,,	Naphthalene	C	0·1	—	(1 : 1) (?)
,,	Phenol	C	,,	—	2 : 1; 1 : 2
Toluene	Phenol	C	,,	—	†
Naphthalene	2-Naphthol	C	,,	—	†

* Solvents: B = benzene; C = carbon tetrachloride; D = dioxan; T = toluene; W = water.
† No evidence of complex formation.

with pairs of donor compounds representative of many intended to be used in later work gives no evidence of (*c*), and the evidence for detection of (*b*) is doubtful for, even in the case of the two complexes between phenol and benzene, the possibility of hydrogen-bond formation cannot be entirely ruled out, because Jones and Badger (*J. Amer. Chem. Soc.*, 1951, **73**, 3132; cf. Badger, *J. Chem. Phys.*, 1940, **8**, 228) obtained infra-red spectro-

photometric evidence of intermolecular hydrogen bonding between methanol and the hydrogen of aromatic rings in benzene and other hydrocarbons in binary solutions in organic solvents. They also consider that the weaker association of phenol in benzene than in carbon tetrachloride may be evidence of a phenol–benzene hydrogen bond (cf. also Mecke, *Discuss. Faraday Soc.*, 1950, **9**, 161).

Subsequent papers will describe a number of other experiments, including studies of the interactions, *e.g.*, of various hydroxylic solutes, including water, with carbohydrates, and with amides and amines.

Conclusions.—(*a*) It is reasonably certain that the method can give valid evidence of the molar ratio of intermolecular complexes in aqueous or non-aqueous solution, and that it may also be capable of detecting intramolecular chelation. (*b*) There is so far no firm evidence that any other than the acid–base and hydrogen-bond types of association are detectable, though this possibility must be allowed for in the interpretation of results.

Advantages of Present Methods.—The present method appears to be somewhat more versatile than most of the commonly used hydrogen-bond detection procedures,* because it can be employed with a very wide variety of solutes and solvents, including water; it requires quite small quantities of material (normally *ca.* 5 mmoles of each solute, though results might be obtained, if necessary, with as little as 0·05 mmole); it is rapid; and it can give information not readily obtained by most of the other methods. In a subsequent paper it will be shown that a qualitative estimate of the relative strength of bonds is possible in some cases; and it is proposed to attempt to obtain quantitative thermodynamic data of bond energies, etc., by this means.

Experimental

Materials.—The organic solvents used were dried by the usual methods, except dioxan, which was of the " specially dried " quality (B.D.H.) used for Karl Fischer titrations.

Instruments and Procedure.—The dielectric-constant meter has been described in Part I (*loc. cit.*). The following refractometers were employed, both with sodium light: Bellingham and Stanley (Abbe type, reading to 10^{-4} unit) and Zeiss (Pulfrich type, reading to 10^{-5} unit). These require respectively *ca.* 0·1 and 1·0 c.c. liquid for each determination. In all cases a mean of at least two or three independent readings (in special cases up to six) was taken for each solution.

Procedure.—The general procedure followed was identical with that described in Part I, some 8—12 or more separate binary solutions of different molar ratios being used for each pair of solutes. Experiments were repeated in many cases where the position of the change of slope on the curve was uncertain, but normally one set of determinations is sufficient. A concentration of 0·1M or 0·25M is normally used, but in special cases 0·01M-solutions have been employed quite satisfactorily.

It is sometimes advisable to warm the solutions slightly after mixing, and allow them to cool again before use. This avoids irregularities due to imperfect mixing of some liquids which are slow to dissolve in each other. Incomplete solution cannot always be detected by eye.

Over certain temperature ranges some of the curves pass from convex to concave, relative to the *x*-axis, and thus at an intermediate temperature there is no evidence of complex formation. Therefore, if it was important to establish the reality of negative results with a particular group in a solute, determinations were made at more than one temperature, or a variety of second solutes was used, in one solvent, since it is unlikely that a fortuitous negative result would be repeated under similar conditions in a variety of systems.

Preparations of Solid Complexes.—Concentrated solutions in toluene of diethylamine and either *p*-nitrophenol or resorcinol, respectively, were mixed and the crystalline precipitates collected, carefully washed with a minimum of ether, and dried *in vacuo*. The *p*-nitrophenol complex separates out at once, that from resorcinol only slowly; the mixed solutions with resorcinol were therefore kept for several days in the cold before the precipitate was collected. *p*-Nitrophenol *complex*, yellow needles, m. p. 90° (Found: C, 54·8; H, 5·9; N, 11·85. $C_{16}H_{21}O_6N_3$ requires C, 54·9; H, 6·0; N, 12·0%). Resorcinol *complex*, buff platelets, m. p. 119° (Found: C, 65·6; H, 8·3; N, 4·81. $C_{16}H_{23}O_4N$ requires C, 65·5; H, 7·85; N, 4·8%).

* See, *e.g.*, Hunter, *Ann. Reports*, 1946, **43**, 141.

Determination of "Apparent Molecular Weight."—The Beckmann f. p. method was used, with "molecular-weight quality" benzene, and a series of 0·1M-binary solutions. The apparent molecular weight is the value calculated on the assumption that only one compound is present, and is equal to the sum of the products of the true molecular weights of each solute multiplied by their respective molar fractions. The points shown in Figs. 7—10 are each the mean of two or three separate determinations.

Some attempts were made to detect bonding between amino-acids and glucose in aqueous solutions by measurement of specific rotation in a polarimeter, but the acids were insufficiently soluble to give any useful result.

The authors express their thanks to Professor P. D. Ritchie for his interest and encouragement, to Miss M. M. Allingham for making the polarimetric experiments, to Mr. S. K. Jain for making some of the experiments shown in Table 3, and to Dr. W. Good, Dr. J. C. Speakman, and Mr. C. Weaver for helpful discussions.

Appendix

(By John C. Eaton, Department of Mathematics, Royal Technical College, Glasgow, C.1.)

Theoretical Treatment of Relation between a Physical Constant and Molar Concentration of Binary Solutions.—A physical property e varies linearly with concentration of a substance X in a given quantity of solvent; *i.e.*,

$$e_1 = e_0 + (x/C)S_X \text{ (cf. } PQ, \text{ Fig. 12)}$$

where e_0 is the value for the pure solvent; C is the total number of molecules at maximum concentration; x is the number of molecules of X at any intermediate point; and S_X is a constant for the substance (of the dimensions of e).

The same is true for a second substance Y; thus

$$e_2 = e_0 + (x/C)S_Y \text{ (cf. } PT, \text{ Fig. 12)}$$

(where S_Y is the constant for the substance Y) except that rate of increase S_Y differs from S_X. If, now, the number of molecules of Y is allowed to vary from C to 0 instead of from 0 to C, then

$$e_3 = e_0 + [(C - x)/C]S_Y \text{ cf. } RS, \text{ Fig. 12)}$$

so that if x molecules of X and $C - x$ molecules of Y are simultaneously dissolved, and there is no interaction between X and Y, *i.e.*, the total number of molecules of X and Y remains constant at C, then

$$e_4 = e_0 + S_Y + (S_X - S_Y)x/C = e_1 + e_3 - e_0$$

This gives the line SQ (Fig. 12; cf. Fig. 3).

Finally if p molecules of X combine with q molecules of Y to form r molecules of X_pY_q (subsequently called XY for clarity), then

$$e_5 = e_0 + (x - pz/r)S_X/C + (C - x - qz/r)S_Y/C + zS_{XY}/C$$

[S_{XY} being the (unknown) value for the complex XY]

$$= e_0 + S_Y + (S_X - S_Y)x/C + (S_{XY} - pS_X/r - qS_Y/r)z/C$$
$$= e_4 + (S_{XY} - pS_X/r - qS_Y/r)z/C$$

so that the deviation of e_5 from the line SQ is proportional to z.

Now z is determined according to the mass-action law:

$$K = z^r/[(x - pz/r)^p\ (C - x - qz/r)^q] \text{ where } K \text{ is the reaction constant,}$$

or $K(x - pz/r)^p\ (C - x - qz/r)^q = z^r$.

Differentiating this with respect to x, z being treated as a function of x, we obtain

$$K[(C - x - qz/r)^q\, p(x - pz/r)^{p-1}\,(1 - pz'/r) + (x - pz/r)^p q\,(C - x - qz/r)^{q-1}\,(-1 - qz'/r)] = rz^{r-1}z'$$

Solving for z', we obtain,

$$z' = \frac{K(x - pz/r)^{p-1}(C - x - qz/r)^{q-1}[Cp - (p+q)x]}{rz^{r-1} - K(x - pz/r)^{p-1}(C - x - qz/r)^{q-1}[(p^2 - q^2)x/r + pq(p+q)z/r^2 - Cp^2/r]}$$

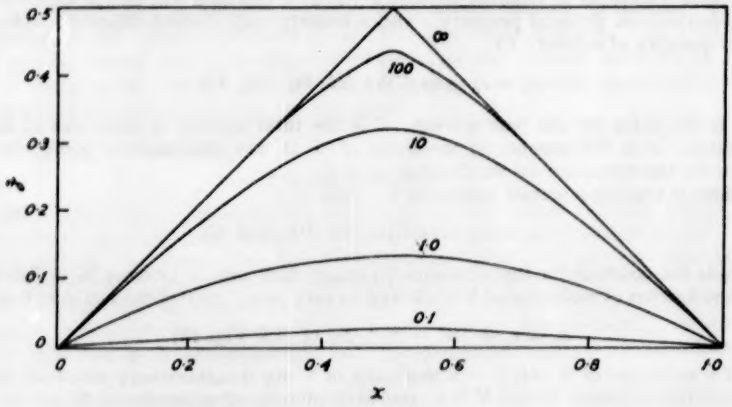
Now p, q, r, x, z, and C are positive integers, and K is also positive, while $x - pz/r > 0$ and $C - x - qz/r > 0$, since otherwise K would be infinite (which, for the moment, we do not consider), so that $z' = 0$ only if $Cp - (p+q)x = 0$, *i.e.*, if $x = pC/(p+q)$.

Consider now the sign of $(p^2 - q^2)x/r + pq(p+q)z/r^2 - Cp^2/r$ (= say, D). The maximum value that z possibly can have is $Cr/(p+q)$, when $Cp/(p+q)$ molecules of X combine with $Cq/(p+q)$ molecules of Y, all of X and Y combining. Over the range $0 \leqslant x \leqslant Cp/(p+q)$, we have

$$\begin{aligned} D &= [(p-q)x/r + pqz/r^2 - Cp^2/r(p+q)](p+q) \\ &\leqslant [(p-q)Cp/r + pqCr/r^2 - Cp^2/r] = 0 \end{aligned}$$

Consider next the range $Cp/(p+q) < x \leqslant C$, which requires $z < (C-x)r/q$.

FIG. 13. *Relation between z and x for the values of K shown on the curves.*



Here

$$\begin{aligned} D &< (p^2 - q^2)x/r + pq(p+q)(C-x)r/qr^2 - Cp^2/r \\ &= (1/r)[pqC - qx(p+q)] \\ &< (1/r)[pqC - q(p+q)Cp/(p+q)] = 0 \end{aligned}$$

Thus D is negative for all values of x except $pC/(p+q)$, when it is zero, and thus the denominator of z', *viz.*,

$$rz^{r-1} - K(x - pz/r)^{p-1}(C - x - qz/r)^{q-1}D$$

is positive for all values of x; z' therefore has the same sign as $Cp - (p+q)x$. Thus z' is positive over the range $0 \leqslant x < pC/(p+q)$, and is negative over the range $pC/(p+q) < x \leqslant C$, *i.e.*, there is a single maximum at $x = pC/(p+q)$, no matter how large p, q, r may be.

When $p = q = r = 1$, the mass-action law leads to a quadratic equation for z, and the graph of z against x is a hyperbola; for larger values of p, q, r, the mass-action law leads to curves of higher degree, but we have shown that they have only one maximum in the range $0 \leqslant x \leqslant C$, and hence $e_5 - e_4$, the deviation from the line SQ, will have only one turning value, a maximum or minimum according as $S_{XY} - pS_X/r - qS_Y/r$ is greater than or less than zero.

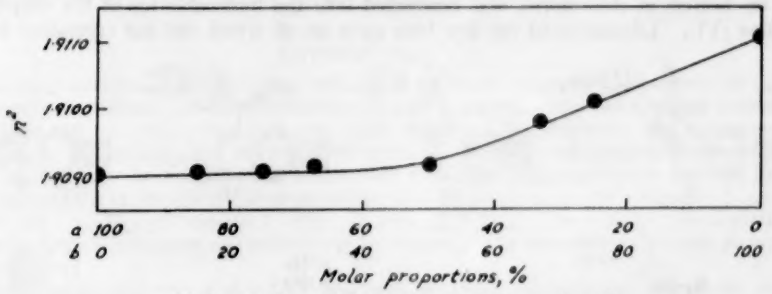
If values of e_5 are determined experimentally for sufficient values of x to determine the graph of e_5 against x accurately, and if the graph is found to be very nearly two straight lines, then the abscissa of their intersection will be close to $pC/(p+q)$, and hence the ratio p/q may be determined.

When $K \to \infty$, whatever the values of p and q the graph becomes a pair of straight lines which intersect at $x = pC/(p+q)$.

It should be noted that if ϵ_3 gives a single straight line SQ, this does not necessarily imply that no interaction takes place, as this result must follow even if there is interaction, provided $rS_{XY} = pS_X + qS_Y$.

Fig. 13 shows the variation in the graph of z against x for different values of K when $p = q = r = 1$. Figs. 6 and 14 show the experimental points for three typical systems giving 1 : 1 complexes. In the systems shown in Fig. 6 the values for K at room temperature are given

FIG. 14. *Theoretical* (curve) *and experimental* (points) *relation between square of refractive index and component ratio in binary solutions.*



a, Methanol; *b*, erythritol; solvent, 2-ethoxyethanol.

by Flett (*loc. cit.*) as 4·80—7·10 for azobenzene + benzyl alcohol and 381—461 for dimethylformamide + phenol, but in the system shown in Fig. 14 the value is unknown and an arbitrary figure of $K = 10$ has been assumed, and from this the value of the constant (n^2), corresponding to S_{XY}, for the complex is then computed from the treatment above, and the theoretical curve obtained thereby is shown.

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Experiments on the Synthesis of Tetrahydroworenine.

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[Reprint Order No. 5676.]

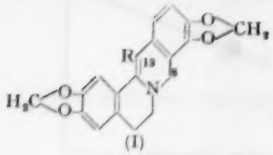
Attempts to synthesise tetrahydroworenine (I; R = Me) led as far as 5 : 6 : 13 : 13*a*-tetrahydro-2 : 3 : 10 : 11-tetrahydroxy-8*H*-dibenzo[*a*, *g*]pyridocoline hydrochloride (cf. XI; R = H), but no further.

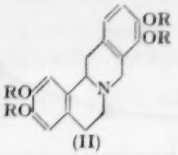
WORENINE, isolated as its tetrahydro-derivative from *Coptis japonica* by Kitasato (*J. Pharm. Soc. Japan*, 1927, No. 542, 28; *Chem. Abs.*, 1927, **21**, 2700), is a homologue of coptisine (I; R = H), whose tetrahydro-derivative has been synthesised (Späth and Posega, *Ber.*, 1929, **62**, 1029); it has been shown not to be the 8-methyl compound (Kitasato, *Acta Phytochim., Tokyo*, 1927, **3**, 175; *Chem. Abs.*, 1928, **22**, 1780), and hence was assigned structure (I; R = Me). Corydaline (II; R = Me) has been synthesised (Späth and Kruta, *Ber.*, 1929, **62**, 1024) by methylating the corresponding tetrahydric phenol, which in turn was prepared from methylenepapaverine (III). It was proposed to prepare compound (II; R = H), and thence the presumed tetrahydroworenine.

3 : 4-Dimethoxyhydratroponitrile was prepared by alkylation of homoveratronitrile, and hydrolysed to the acid, which had previously been prepared by Bougault from methyleugenol (*Ann. Chim.*, 1902, **25**, 562). The alkylation gave a quantity of oil as well as the crystalline nitrile, and hydrolysis of the oily mixture gave an oily acidic fraction, and a crystalline neutral compound. Separation of the acids by fractional liberation from their sodium salts gave, in order of increasing basicity, α-(3 : 4-dimethoxyphenyl)*iso*butyric acid (IV; R = Me), 3 : 4-dimethoxyhydratropic acid (IV; R = H), and homoveratric acid,

the first of these being present in relatively small amount. The neutral compound could also be prepared by treating α-(3 : 4-dimethoxyphenyl)*iso*butyric acid with thionyl chloride, then with ammonia, showing it to be the corresponding amide. The neutral compound gave analyses consistently and accurately two hydrogen atoms short for the amide, probably owing to the splitting off of methane from the *gem*-dimethyl group during combustion.

Reaction of 3 : 4-dimethoxyhydratropoyl chloride with 2-(3 : 4-dimethoxyphenyl)-ethylamine gave the amide (V), which on treatment with phosphorus oxychloride, either alone or, better, in chloroform, was converted into the hydrochloride of the dihydro*iso*-quinoline (VI). Liberation of the free base gave an oil which did not crystallise but on


(I)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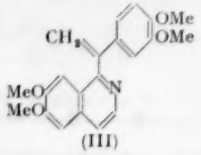
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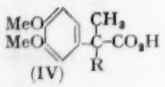
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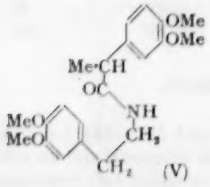
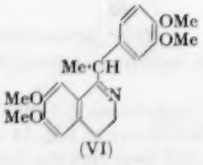
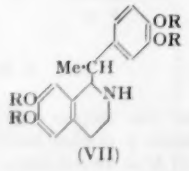
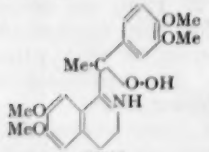

(V)

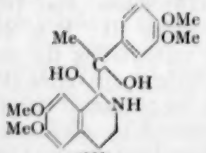

(VI)

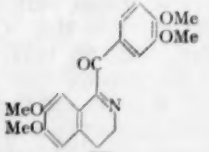

(VII)

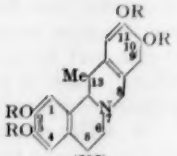
exposure in ethereal solution to air gave an unstable crystalline material; this may be (VIII) or less probably (IX); its colour reaction with acetic anhydride is similar to that of the ketone (X) prepared by aerial oxidation of the corresponding 1-(3 : 4-dimethoxybenzyl) derivative (Buck, Perkin, and Stevens, *J.*, 1925, 1470). Reduction of the dihydro*iso*-quinoline hydrochloride with Adams catalyst in dilute hydrochloric acid gave the hydrochloride of the tetrahydro*iso*quinoline (VII; R = Me).

For comparison, the hydrochloride of the tetrahydric phenol (XI; R = H) was prepared by condensing the tetrahydro*iso*quinoline (VII; R = Me) with formaldehyde, and demethylating the product with hydriodic acid and red phosphorus, and replacing the iodide ion by chloride ion. Similar demethylation of the *iso*quinoline (VII; R = Me) gave the hydrochloride of the phenol (VII; R = H), previously prepared by Späth and Kruta (*loc. cit.*), but not well characterised: it was unusually sensitive to oxidation. Condensation of the phenol (VII; R = H) with a slight excess of formaldehyde was accompanied by a marked colour change, and under the conditions used by Späth and Kruta (*loc. cit.*), a good yield of a highly crystalline product was generally obtained. Attempts to carry out the reaction under physiological conditions gave only amorphous material, as did one of a series of identical runs under Späth and Kruta's conditions. The reason for this is not known.


(VIII)


(IX)


(X)


(XI)

Though the only crystalline material Späth and Kruta obtained by methylation of this product was corydaline (II; R = Me), it is likely that the condensation with formaldehyde yielded a mixture of the hydrochlorides of (XI and II; R = H). The evidence from the very indefinite melting points is of no help in this matter; the compounds became

increasingly gummy with rising temperature, and the melting points recorded may, in fact, be the temperatures at which the compounds dissolved in their water of crystallisation.

Attempts to introduce the methylenedioxy-group into the free base by means of methylene halides or methylene sulphate were unsuccessful, and attempts to brominate the compound (XI; R = H) to the tetrabromo-derivative, with a view to oxidising the product to the bis-*o*-quinone which could be treated with diazomethane (cf. Horner and Lingnau, *Annalen*, 1951, **573**, 30), resulted in the destruction of the compound before the theoretical amount of bromine had been taken up.

Experimental

Alkylation of Homoveratronitrile.—To a solution of sodamide, prepared from sodium (4·3 g.), in liquid ammonia (500 c.c.) homoveratronitrile (30 g.) was added. After 10 minutes' swirling, methyl iodide (14 c.c.) was added dropwise, with swirling. The ammonia was evaporated, water added to the residue, and the insoluble material collected and pressed between filter papers to remove oil. Recrystallisation of the solid from light petroleum (b. p. 40—60°) gave rhombic tablets of 3 : 4-*dimethoxyhydratroponitrile* (16·7 g., 52%), m. p. 71° (Found : C, 68·9; H, 6·9; N, 7·6. $C_{11}H_{13}O_2N$ requires C, 69·1; H, 6·8; N, 7·3%). The yield in this alkylation was unchanged when potassium was substituted for sodium. The treatment of the oily material is described later.

3 : 4-*Dimethoxyhydratropic Acid.*—This acid was produced by refluxing the nitrile with aqueous-ethanolic sodium hydroxide till ammonia ceased to be evolved (about 20 hr.). The ethanol was evaporated, an excess of hydrochloric acid added, and the acid extracted with ether. Evaporation of the dried extract left the acid as an oil which was recrystallised from light petroleum (b. p. 40—60°), giving ill-defined plates, m. p. 50°, of the anhydrous acid (Found : C, 63·0; H, 6·8. Calc. for $C_{11}H_{14}O_4$: C, 62·9; H, 6·7%); Bougault (*loc. cit.*) gives m. p. 50°, but says that it can be obtained crystalline only by dehydrating a crystalline sample of the monohydrate.

N-1-(3 : 4-*Dimethoxyphenylethyl*)-3 : 4-*dimethoxyhydratropamide* (V).—The crude acid from 13·4 g. of nitrile was refluxed with thionyl chloride (20 c.c.) in chloroform (25 c.c.) for 1 hr., the chloroform evaporated, and the residual thionyl chloride removed by evaporation with toluene. The acid chloride was taken up in dry ether and added to 2-(3 : 4-dimethoxyphenyl)-ethylamine (12 g.) in dry pyridine–ether (30 + 200 c.c.). Next day sufficient chloroform and water were added to dissolve all precipitated material, and the non-aqueous phase was washed with dilute hydrochloric acid, sodium carbonate solution, and water. Evaporation of the dried solvents left crude N-1-(3 : 4-*dimethoxyphenylethyl*)-3 : 4-*dimethoxyhydratropamide* (17·6 g., 70% based on the nitrile). Recrystallisation from toluene gave needles, m. p. 117° (Found : C, 67·7; H, 7·2; N, 3·9. $C_{21}H_{27}O_5N$ requires C, 67·6; H, 7·2; N, 3·8%).

1-[1-(3 : 4-*Dimethoxyphenyl*)*ethyl*]-3 : 4-*dihydro*-6 : 7-*dimethoxyisoquinoline Hydrochloride* (VI).—A mixture of the foregoing amide (3·6 g.) and phosphorus oxychloride (30 c.c.) was refluxed for 45 min., then evaporated under reduced pressure on the water-bath. To the residue ice and dilute hydrochloric acid were added, the mixture was filtered, and the filtrate was extracted with ether. The acid liquor was made alkaline with aqueous sodium hydroxide, the base extracted with ether, then re-extracted with dilute hydrochloric acid, and this procedure repeated. The acid liquid gradually deposited the required *hydrochloride* (2·9 g.) as yellow crusts. Repeated recrystallisation from dilute hydrochloric acid gave hygroscopic yellow needles, m. p. 91—93° (Found : C, 63·9; H, 7·0; N, 3·7; Cl, 8·9. $C_{21}H_{26}O_4NCl$ requires C, 64·4; H, 6·6; N, 3·6; Cl, 9·1%). In later runs a mixture of phosphorus oxychloride (1 part) and chloroform (3 parts) was used, refluxing continued for 2 hr., and during subsequent working up, the temperature kept below 70°; a cleaner product was so obtained. The *methiodide*, which was very soluble in methanol or acetone, crystallised from acetone–ether in yellow nodules, m. p. 173° (slight decomp.) (Found : I, 25·7. $C_{22}H_{28}O_4NI$ requires I, 25·5%).

Attempts to isolate the free base gave an oil, which did not crystallise even when its solution in ether was stored at 0° for several weeks. Exposure of its solutions in moist ether to the air caused the separation of colourless needles. This material was unstable, decomposing on storage or on being heated in solution, and had m. p. 90—110° (decomp.), depending on rate of heating {Found, on two samples : (i) (crystallised from ether), C, 64·9; H, 7·1; (ii) [crystallised from benzene–light petroleum (b. p. 60—80°)], C, 65·5; H, 7·0. $C_{21}H_{25}O_4N$ requires C, 65·1; H, 6·5. $C_{21}H_{27}O_4N$ requires C, 64·8; H, 6·9%}. The substance gave a yellow solution in dilute

hydrochloric acid; its solution in acetic anhydride was deep yellow at first, but faded on boiling, then became intense green.

1-[1-(3 : 4-*Dimethoxyphenyl*)*ethyl*]-1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy*iso*quinoline Hydrochloride* (VII; R = H).—A solution of the corresponding dihydroisoquinoline in dilute hydrochloride acid was shaken with hydrogen in presence of Adams platinum oxide till uptake of hydrogen ceased. After filtration from the catalyst, evaporation of the solution gave the *hydrochloride* of the tetrahydro-base as needles, m. p. *ca.* 108° (Found: C, 63·6; H, 7·6; N, 3·6; Cl, 8·9. $C_{21}H_{28}O_4NCl$ requires C, 64·0; H, 7·1; N, 3·6; Cl, 9·0%). Acetylation with acetic anhydride and pyridine in the cold gave an *acetyl derivative*, as felted needles (from methanol), m. p. 151° (Found: C, 69·0; H, 7·2; N, 3·8. $C_{23}H_{29}O_5N$ requires C, 69·2; H, 7·2; N, 3·5%).

5 : 6 : 13 : 13a-*Tetrahydro*-2 : 3 : 10 : 11-*tetramethoxy*-13-*methyl*-8H-*dibenzo*[a, g]*pyridocoline* (XI; R = Me) (Ring Index no. 2703).—The preceding hydrochloride (0·8 g.), concentrated hydrochloric acid (1 c.c.), water (5 c.c.), and 40% aqueous formaldehyde (2·4 c.c.) were heated on the water-bath for 45 min., the solution was evaporated, and the residue taken up in water. Addition of aqueous sodium hydroxide in excess, followed by extraction with chloroform and evaporation of the solvent, left a crystalline residue. Recrystallisation from methanol gave the *dibenzopyridocoline* as tablets (0·65 g.), m. p. 150° (decomp.) (Found: C, 71·5; H, 7·2; N, 4·0. $C_{22}H_{27}O_4N$ requires C, 71·6; H, 7·3; N, 3·8%). The *hydrochloride* was very soluble in water, and was obtained by treatment of a solution of the free base in dry ether with dry hydrogen chloride as a somewhat hygroscopic white powder, m. p. 150—165° (Found: C, 64·9; H, 7·1; N, 3·5; Cl, 8·5. $C_{22}H_{28}O_4NCl$ requires C, 65·0; H, 6·9; N, 3·5; Cl, 8·8%).

5 : 6 : 13 : 13a-*Tetrahydro*-2 : 3 : 10 : 11-*tetrahydroxy*-13-*methyl*-8H-*dibenzo*[a,g]*pyridocoline Hydrochloride* (XI; R = H).—The above base (0·5 g.) was boiled under reflux with concentrated hydriodic acid (7 c.c.) and red phosphorus for 6 hr., the solution evaporated *in vacuo* on a water-bath, and the residue taken up in water and treated with excess of silver chloride. After filtration from the silver salts, the solution was concentrated, and the phenol *hydrochloride* (0·32 g., 68%) was deposited as prisms which on being dried *in vacuo* collapsed to a white powder, m. p. *ca.* 213° (shrinking from 200°), which tenaciously retained one molecule of water of crystallisation (Found, in a sample dried for 6 hr. at 100° *in vacuo*: C, 59·5; H, 6·1; N, 3·9; Cl, 9·7. $C_{22}H_{26}O_4NCl,H_2O$ requires C, 58·8; H, 6·0; N, 3·8; Cl, 9·7%). In attempts to brominate this compound in dilute aqueous or acetic acid solution containing free hydrobromic acid, less than 2 mols. of bromine were taken up. Evaporation of the solutions left brown materials from which small amounts of crystalline products could be isolated.

1 : 2 : 3 : 4-*Tetrahydro*-6 : 7-*dihydroxy*-1-[1-(3 : 4-*dihydroxyphenyl*)*ethyl*]iso*quinoline* (cf. Späth and Kruta, *loc. cit.*).—The compound was prepared by demethylation of the tetramethoxyisoquinoline with hydriodic acid and red phosphorus, followed by conversion into the hydrochloride. This salt, crystallised from dilute hydrochloric acid, had m. p. 241° (decomp.) (lit., 241°); it was very sensitive to oxidation, and with ferric chloride gave a green colour, which rapidly changed through red to purple, the colours becoming more intense (Found: C, 60·4; H, 6·1; N, 4·0; Cl, 10·5. Calc. for $C_{17}H_{20}O_4NCl$: C, 60·5; H, 5·9; N, 4·1; Cl, 10·5%). With cold acetic anhydride and pyridine it gave a *penta-acetyl derivative*, as prisms (from methanol–ether), m. p. 137° (Found: C, 63·5; H, 6·0; N, 2·7. $C_{27}H_{29}O_9N$ requires C, 63·4; H, 5·7; N, 2·9%).

Condensation of the Phenol with Formaldehyde (cf. Späth and Kruta, *loc. cit.*).—The foregoing phenol hydrochloride (1·46 g.) in water (40 c.c.) was heated with 5% aqueous formaldehyde (2·20 c.c.) in a sealed tube at 100° for 5 hr. Immediately on addition of the formaldehyde, the solution became orange, but soon changed to purple, then intense yellow. At room temperature the purple lasted several hours, but at 100° the change was complete in less than 15 min. The liquid was filtered hot from traces of dark amorphous material, and acidified with hydrochloric acid. Grey prisms (1·34 g.) were deposited, which after two recrystallisations from very dilute hydrochloric acid formed white prisms, m. p. 194—196° (shrinking from 180°); mixed with the hydrochloride of (XI; R = H), it melted at *ca.* 205°. The crystals, which tenaciously retained water, did not collapse on being dried, as did those of the hydrochloride of (XI; R = H) (Found: in a sample dried for 12 hr. at 100° *in vacuo*: C, 58·8; H, 5·6; N, 4·2; Cl, 10·7. Calc. for $C_{18}H_{20}O_4NCl,H_2O$: C, 58·8; H, 6·0; N, 3·8; Cl, 9·7%).

(ii) A solution of the hydrochloride (0·33 g.) and 5·85% aqueous formaldehyde (0·55 c.c.) in air-free water (100 c.c.) was kept at room temperature for 2 days under carbon dioxide. This solution, which remained at pH 5·5, showed the colour changes described above, but yielded only amorphous material on concentration. Longer duration of the experiment gave an identical result.

Isolation of α-(3 : 4-*Dimethoxyphenyl*)iso*butyric Acid and its Amide.*—The oily material collected from a number of alkylations (p. 81) was boiled with sodium hydroxide solution till ammonia evolution ceased. An oil remained undissolved, which crystallised under ether. Recrystallisation from ether (first analysis), in which it was very sparingly soluble, or from benzene (second analysis), gave the amide as needles, m. p. 137° (Found: C, 65·1, 65·0; H, 6·9, 6·9; N, 6·1, 6·4. $C_{12}H_{17}O_3N$ requires C, 64·6; H, 7·6; N, 6·3%).

The acids were liberated and partly crystallised during several weeks at −20°. They neutralised 37·7 c.c. of N-sodium hydroxide, and from this solution they were fractionally liberated into chloroform by addition of 11 portions of acid, the last portion being an excess. Each chloroform extract was evaporated, and the residue taken up in light petroleum (b. p. 40—60°), and set aside to crystallise. Fractions 6—11 showed increasing insolubility, and crystallised fairly readily; the others tended to deposit an oil with the crystals. Fractions 8—11 gave homoveratric acid, fractions 1—6 gave 3 : 4-dimethoxyhydratropic acid. In fractions 1—4 there appeared prisms, which were hand-picked and recrystallised from carbon tetrachloride–light petroleum (b. p. 40—60°), to give α-(3 : 4-*dimethoxyphenyl*)iso*butyric acid* as prisms, m. p. 80—81° (Found: C, 64·3; H, 7·1. $C_{12}H_{16}O_4$ requires C, 64·3; H, 7·1%). Treatment of this acid with thionyl chloride in light petroleum (b. p. 80—100°), followed by concentrated aqueous ammonia, gave the amide, as needles (from benzene), m. p. 136°, undepressed on admixture with a sample isolated as described above.

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GLASGOW UNIVERSITY. [*Received, August 23rd,* 1954.]

Aromatic Substitution meta *to a Basic Group. Part II.* Halogenation of Diphenylmethane Derivatives.*

By JOHN H. GORVIN.

[Reprint Order No. 5718.]

Halogenation of di-*p*-amino- and di-*p*-methylamino-phenylmethane in concentrated sulphuric acid in presence of silver ions has given products in which the chlorine or bromine atom lies *meta* to the basic group. Syntheses by alternative procedures have confirmed the orientation. During this work the nuclear bromination of di-*p*-nitrophenylmethane was readily achieved by the cationoid procedure whereas more usual methods produced di-*p*-nitrophenylmethyl bromide. A brief study was made of the behaviour of di-*p*-nitrophenylmethyl derivatives in concentrated sulphuric acid: no evidence was obtained for any substantial degree of ionisation. A new instance of thermal dismutation is recorded.

WHEN di-*p*-amino- and di-*p*-methylamino-phenylmethane were halogenated in concentrated sulphuric acid in the presence of silver ions the substituents entered predominantly the position ***meta*** to the basic groups. Each of the two bases was chlorinated and brominated at about the same rate as the corresponding tertiary amine (Part I) but the crude dihalogeno-compounds, produced in theoretical yield, contained side-products which were difficult to eliminate: purified acetyl derivatives of the 2 : 2′-dihalogeno-compounds were obtained only after tedious recrystallisation and in reduced yield. The greater degree of purity of the products obtained from bis-*p*-dimethylaminophenylmethane (Part I) is noteworthy, and may be because any tendency towards halogenation ***ortho*** to the basic group, either under the influence of a halogen atom already substituted in a ***meta***-position or as a result of a residual ***ortho***-directing effect exerted by the basic group, will be reduced in the dimethylamino-compound by the steric effect of the *N*-methyl groups. In general it would seem that halogenation ***meta*** to the $-NH_3^+$ and $-NH_2{\cdot}CH_3^+$ groups, now demonstrated for the first time, is more limited in its practical application than is the corresponding ***meta***-halogenation of tertiary amines. This is especially true for amines unsubstituted in the ***para***-position since, on analogy with the results of Part I, halogenation of aniline or

* "*p*-Aminodimethylaniline. Part VI" (*J.*, 1953, 1237) is regarded as Part I.

N-methylaniline in sulphuric acid would result in intractable mixtures in which the *m*-halogeno-derivative would inevitably be accompanied by the *para*- and probably the *ortho*-isomer, some dihalogeno-compound, and an equivalent amount of unchanged amine.

The condensation of a *m*-halogeno-aniline with formaldehyde (cf. Wagner, *J. Amer. Chem. Soc.*, 1934, **56**, 1944) provided one alternative route to the di-(4-amino-2-halogenophenyl)methanes : the 2 : 2′-dichloro-compound was obtained in 28% yield by this process. The structures of the two di-(2-halogeno-4-methylaminophenyl)methanes were similarly confirmed by their direct synthesis from *m*-chloro- and *m*-bromo-*N*-methylaniline.

By use of the Sandmeyer procedure the two di-(4-amino-2-halogenophenyl)methanes were obtained from the accessible di-(4-acetamido-2-aminophenyl)methane but the diazonium decompositions gave very low yields of dihalogeno-compound. The di-(4-amino-2-halogenophenyl)methanes were most advantageously prepared by reduction of the appropriate nitro-compound, obtained by cationoid halogenation of di-*p*-nitrophenylmethane in sulphuric acid. The chlorination, like that of di-*p*-aminophenylmethane, initially yielded an impure product requiring tedious recrystallisation; the bromination on the other hand gave an excellent yield of di-(2-bromo-4-nitrophenyl)methane of a high degree of purity. This distinction in the behaviour of the two halogens is compatible with the requirements of the Holleman series for steric impedance of entering groups.

The ease with which di-*p*-nitrophenylmethane undergoes electrophilic bromination in concentrated sulphuric acid stands in sharp contrast to the difficulty of producing this type of reaction in solvents of relatively low ionising power. Under these conditions homolytic bromination in the α-paraffinic position is favoured, as in other benzyl derivatives, owing to the possibility of resonance stabilisation of the di-*p*-nitrophenylmethyl radical initially produced. Thus, in boiling carbon tetrachloride, no product of nuclear bromination was isolated after 7 days' treatment with bromine in the dark in presence of iodine; unchanged di-*p*-nitrophenylmethane (22%) was recovered and the main product (41%) was di-*p*-nitrophenylmethyl bromide, previously obtained by Orazi and Giunti (*Anal. Asoc. Quím. Argentina*, 1951, **39**, 89) by bromination with 1 : 3-dibromo-5 : 5-dimethylhydantoin under irradiation. Under strong illumination bromination in carbon tetrachloride proceeded rapidly to give initially the methyl bromide and, with a second molecule of bromine, dibromodi-*p*-nitrophenylmethane. A similar reaction took place in boiling acetic acid, but the end-product was then 4 : 4′-dinitrobenzophenone (84%) produced by hydrolysis of the dibromide. These observations serve to emphasise the value of Derbyshire and Waters's procedure (*J.*, 1950, 573) in the achievement of nuclear halogenation of compounds preferentially attacked by atomic halogen under ordinary conditions; the ready electrophilic halogenation in sulphuric acid evidently depends on a more powerful evocation by the Br^+ cation, as compared with the formally neutral Br_2 molecule, of a polarisability effect in the ring (cf. de la Mare, *J.*, 1949, 2872).

In di-*p*-nitrophenylmethyl bromide the ionising tendency common to diphenylmethyl derivatives (cf. Burton and Praill, *Quart. Reviews*, 1952, **6**, 302; Gillespie and Leisten, *ibid.*, 1954, **8**, 50) must be near a minimum, since the *p*-nitro-groups strongly oppose the stabilisation of a carbonium ion; this does not of course preclude reaction by an ionic mechanism under favourable conditions. Whereas both diphenylmethyl bromide and its di-*p*-bromo-derivative (Goldthwaite, *Amer. Chem. J.*, 1903, **30**, 450) dissolve in concentrated sulphuric acid, showing the intense orange-red colour characteristic of a stable carbonium ion, the di-*p*-nitro-compound formed a pale yellow solution from which it could be recovered on dilution with water. Addition of silver sulphate to the sulphuric acid solution, however, caused immediate precipitation of silver bromide and, after removal of this, the filtrate remained clear on addition to ice : it evidently contained the un-ionised hydrogen sulphate, for acid hydrolysis gave di-*p*-nitrophenylmethanol or, in concentrated solution, a mixture of this with bisdi-*p*-nitrophenylmethyl ether. 4 : 4′-Dinitrobenzophenone was produced on alkaline hydrolysis owing to ready oxidation of the alcohol. Curtin and Leskowitz (*J. Amer. Chem. Soc.*, 1951, **73**, 2632) have obtained this alcohol by reduction of 4 : 4′-dinitrobenzophenone, and converted it into the ether by the use of toluene-*p*-sulphonic acid : in the present work it was noticed that crystals of the alcohol which had separated from a dilute solution in sulphuric acid occluded sufficient of the acid

to catalyse elimination of water at the melting point with rapid resolidification as the ether, whereas after one recrystallisation from aqueous acetic acid there was no apparent change on melting. The mechanism of this acid-catalysed self-etherification is presumably represented by the equations of Burton and Cheeseman (*J.*, 1953, **832**, 986) which require the transitory existence of a carbonium ion. Di-*p*-nitrophenylmethanol differs, however, from such compounds as di-*p*-methoxyphenylmethanol (Balfe, Kenyon, and Thain, *J.*, 1952, 790) and dimesitylmethanol (Fuson and Jackson, *J. Amer. Chem. Soc.*, 1950, **72**, 351) in reacting in general as a normal secondary alcohol. Its solution in concentrated sulphuric acid was pale yellow, in contrast to the intense colours shown by analogous solutions containing the diphenylmethylium ion (Welch and Smith, *J. Amer. Chem. Soc.*, 1950, **72**, 4748) or its di-*p*-chloro-derivative (Newman and Deno, *ibid.*, 1951, **73**, 3646), and evidently contained the un-ionised hydrogen sulphate since the alcohol was regenerated when the colourless solution obtained on addition to ice was heated. Acetic acid had no appreciable action on the alcohol and hot acetic anhydride reacted rather slowly to give the acetate, also readily obtained from the bromide by the action of silver acetate in acetic acid. Both the ether and the acetate gave pale yellow solutions in concentrated sulphuric acid which remained clear when poured on ice: the alcohol was regenerated when the resultant aqueous solution was heated. Dibromodi-*p*-nitrophenylmethane similarly dissolved in sulphuric acid to give a pale yellow solution, but this slowly evolved hydrogen bromide, and gave 4 : 4′-dinitrobenzophenone when added to ice.

Since tri-*p*-nitrophenylmethanol is converted into the coloured carbonium ion in 80—95% sulphuric acid (Westheimer and Kharasch, *J. Amer. Chem. Soc.*, 1946, **68**, 1874; Lowen, Murray, and Williams, *J.*, 1950, 3318, 3322; Newman and Deno, *loc. cit.*) it was of interest to record the behaviour of di-*p*-nitrophenylmethyl derivatives in media of even higher acidity. The pale yellow colour shown by di-*p*-nitrophenylmethyl bromide and the methanol in concentrated sulphuric acid was noticeably intensified in 20% oleum or chlorosulphonic acid but only to a qualitatively similar degree to the enhancement of the pale yellow colour of di-*p*-nitrophenylmethane in the same solvents: the effect may therefore be due to more complete protonation of the nitro-groups (Gillespie, *J.*, 1950, 2547) rather than to stabilisation of the carbonium ion.

These general conclusions are upheld by the observation by Welch and Smith (*J. Amer. Chem. Soc.*, 1953, **75**, 1412) that di-*p*-nitrophenylacetic acid gives a stable pale yellow solution in 100% sulphuric acid whereas diphenylacetic acid and its di-*p*-chloro-derivative react to form the carbonium ion with loss of carbon monoxide.

When bisdi-*p*-nitrophenylmethyl ether was heated under reduced pressure it dismutated near its melting-point to a mixture of di-*p*-nitrophenylmethane and 4 : 4′-dinitrobenzophenone. The change did not appear to be catalysed by occluded hydrogen ions (cf. Burton and Cheeseman, *J.*, 1953, 986) as it occurred readily in a sample of bis-ether which had been recrystallised from alcoholic pyridine. Thermal dismutation of diphenylmethyl derivatives has been reported by Nef (*Annalen*, 1897, **298**, 234), Goldthwaite (*Amer. Chem. J.*, 1903, **30**, 462), and Bacon (*ibid.*, 1905, **33**, 90), and may proceed by a free-radical mechanism.

Experimental

*Halogenation of Di-*p*-aminophenylmethane in Sulphuric Acid.*—(*a*) *Bromination.* A solution of the base (1·98 g.) and silver sulphate (3·12 g.) in concentrated sulphuric acid (25 c.c.) was shaken with bromine (3·2 g.). Heat was evolved and after 30 min. the theoretical amount of silver bromide was obtained on filtration. The filtrate was poured into ice–water containing sodium sulphite, and neutralised. On extraction with ether the crude product was obtained as a glass (3·4 g., 96%) which, when treated with acetic anhydride in acetic acid, gave an acetyl derivative (4·2 g.), m. p. *ca.* 215°. Six recrystallisations from ethanol reduced the yield to 0·55 g., and the material had m. p. 233° and 239° (dimorphic forms) undepressed on admixture with di-(4-acetamido-2-bromophenyl)methane, m. p. 236° and 243° (see below). The crude base, treated in ethanol with hydrochloric acid, very slowly deposited a hydrochloride which gave impure di-(4-amino-2-bromophenyl)methane on basification: the procedure was not, however, an effective method of purification.

(*b*) *Chlorination.* A solution of the base (1·98 g.) and silver sulphate (3·12 g.) in concentrated

sulphuric acid (40 c.c.) was shaken with excess of dry chlorine in a stoppered 1 l. flask fitted with a tap. After 4 hr. pressure ceased to fall. The excess of chlorine was removed and the acid solution poured into ice–water containing sodium sulphite. After removal of silver chloride the filtrate was neutralised and the crude product (2·6 g., 100%) extracted with ether. Acetylation of the oil and three crystallisations from aqueous ethanol or from acetic acid gave a product (2·2 g., 62%), m. p. 220° and 224—225° (dimorphic forms) not depressed by di-(4-acetamido-2-chlorophenyl)methane, m. p. 226—227° (see below).

*Halogenation of Di-*p*-methylaminophenylmethane in Sulphuric Acid.*—(*a*) *Bromination.* The base (2·26 g.; m. p. 55—56°), prepared according to von Braun (*Ber.*, 1908, **41**, 2148; cf. Wagner, *loc. cit.*), was brominated under the foregoing conditions. After 30 min. the theoretical amount of silver bromide was recovered. The oily product (94%) gave a crude acetyl derivative (2·7 g., 58%), m. p. 126—128° (from aqueous ethanol). Further crystallisation gave *di-(2-bromo-4-N-methylacetamidophenyl)methane* in needles or flakes, m. p. 131·5—132·5°, very soluble in ethanol and acetic acid (Found : Br, 34·2. $C_{19}H_{20}O_2N_2Br_2$ requires Br, 34·1%). *Di-(2-bromo-4-methylaminophenyl)methane*, produced on treatment of the acetyl derivative with warm concentrated hydrochloric acid for 12 hr., initially formed a glass, but crystals, m. p. 76—77·5°, were obtained from petroleum (b. p. 90—120°) (Found : N, 7·3; Br, 41·5. $C_{15}H_{16}N_2Br_2$ requires N, 7·3; Br, 41·6%).

(*b*) *Chlorination.* The base (2·26 g.) was chlorinated within 4 hr. under the foregoing conditions, recovery of silver chloride being quantitative. The oily product (2·86 g., 97%) was converted into its acetyl derivative which gave crystals (2·08 g., 55%), m. p. 114—116°, from aqueous ethanol. Recrystallisation gave *di-(2-chloro-4-N-methylacetamidophenyl)methane* in flakes, m. p. 120—121° (Found : C, 60·0; H, 5·3; N, 7·4; Cl, 18·8. $C_{19}H_{20}O_2N_2Cl_2$ requires C, 60·2; H, 5·3; N, 7·4; Cl, 18·7%).

Condensations with Formaldehyde.—(*a*) m-*Chloroaniline.* A solution of the base (5·9 g.) in ethanol (100 c.c.), concentrated hydrochloric acid (6·6 c.c.), and aqueous formaldehyde (1·74 g.) was refluxed for 65 hr. The mixture was basified, steam-distilled, and then extracted with ether. The resulting oil was distilled twice at *ca.* 240°/0·5 mm., much resin remaining in the flask. The distillate (2·5 g.), when dissolved in ethanol and treated with concentrated hydrochloric acid (2 c.c.), gave a hydrochloride from which di-(4-amino-2-chlorophenyl)methane (1·73 g., 28%), m. p. 100—102°, was obtained on basification : there was no depression in m. p. on admixture with the material, m. p. 102·5—103·5°, described below.

(*b*) m-*Chloro*-N-*methylaniline.* The toluene-*p*-sulphonyl derivative (19·8 g.) of *m*-chloroaniline, dissolved in warm 10% sodium hydroxide (65 c.c.) and ethanol, was methylated with methyl sulphate (19·5 c.c.), the addition being repeated twice with half-quantities of reagent. The slightly alkaline mixture was cooled with agitation and the solid (20·5 g.), m. p. 77—79°, filtered off and hydrolysed by refluxing it with 75% sulphuric acid (75 c.c.) for 2½ hr. Unchanged material was removed with ether, and the *m*-chloro-*N*-methylaniline extracted from the basified solution and distilled at 234°/760 mm. (von Braun and Kruber, *Ber.*, 1913, **46**, 3474, gave b. p. 235°) : the yield was 87%. The base (6·8 g.) was condensed with formaldehyde by the foregoing method during 17 hr., and the resulting oil (5·7 g.) distilled three times at 240—250°/0·3 mm. to separate *di-(2-chloro-4-methylaminophenyl)methane* (3·8 g., 54%) from accompanying resin. The product formed prisms, m. p. 73—74·5°, from light petroleum (b. p. 60—80°) (Found : C, 61·2; H, 5·6; Cl, 24·1. $C_{15}H_{16}N_2Cl_2$ requires C, 61·05; H, 5·5; Cl, 24·0%). Its dihydrochloride, decomp. *ca.* 185°, was very soluble in ethanol from which it was precipitated by ether. On acetylation the base gave di-(2-chloro-4-*N*-methylacetamidophenyl)methane, m. p. 120—121°, not depressed by the material previously described.

(*c*) m-*Bromo*-N-*methylaniline.* The toluene-*p*-sulphonyl derivative (16·7 g.) of *m*-bromoaniline, methylated by the foregoing procedure, gave 17·0 g. of product, m. p. *ca.* 85°. Hydrolysis yielded m-*bromo*-N-*methylaniline* as an oil, b. p. *ca.* 253°/760 mm., which darkened rather rapidly in air (Found : Br, 42·7. C_7H_8NBr requires Br, 42·9%) : the *picrate* crystallised in yellow needles, m. p. 140—141°, from ethanol (Found : C, 38·0; H, 2·7; Br, 19·0. $C_{13}H_{11}O_7N_4Br$ requires C, 37·6; H, 2·7; Br, 19·25%). The base was condensed with formaldehyde during 17 hr. Purification of the partly resinous product presented considerable difficulty as further resinification appeared to occur on distillation at 0·4 mm. Fractional extraction and crystallisation from light petroleum (b. p. 60—80° and 40—60°) eventually gave a specimen of di-(2-bromo-4-methylaminophenyl)methane, m. p. 76—77°, which yielded a di-*N*-acetyl derivative, m. p. 131·5—132·5°. There was no depression on admixture with the compounds described previously.

Sandmeyer Reactions with Di-(4-acetamido-2-aminophenyl)methane.—(*a*) The base (5·4 g.)

(cf. Ehrlich and Bauer, *Ber.*, 1915, **48**, 505), diazotised in suspension in 24% hydrobromic acid (40 c.c.) with sodium nitrite, was poured into a hot solution of cuprous bromide (excess) in 48% hydrobromic acid. After the vigorous reaction had subsided the solution was cooled, filtered from a solid tar, and made strongly ammoniacal. The resulting precipitate separated from aqueous ethanol (charcoal) as a crystalline powder (0·07 g.), m. p. *ca.* 107° and 129° (dimorphic), and on acetylation gave di-(4-acetamido-2-bromophenyl)methane, m. p. 235° and 241° (dimorphic) not depressed by either of the specimens described elsewhere.

(*b*) The base (5·4 g.) was diazotised in hydrochloric acid, and the solution added to cuprous chloride in hot concentrated hydrochloric acid. A small amount of amine, m. p. 96—98°, was isolated which on acetylation gave di-(4-acetamido-2-chlorophenyl)methane, m. p. 218° and 222—223° not depressed by either of the specimens described elsewhere.

*Halogenation of Di-*p*-nitrophenylmethane in Sulphuric Acid.*—(*a*) *Bromination.* A solution of the dinitro-compound (5·16 g.) and silver sulphate (6·3 g.) in concentrated sulphuric acid (18 c.c.) and water (2 c.c.) was shaken with bromine (6·5 g.) for 3 hr. The solution was poured into ice–water and the collected precipitate extracted with methanol to give *di-*(2-*bromo*-4-*nitrophenyl*)*methane* (7·8 g., 94%; m. p. *ca.* 151°). Crystallisation from acetic acid and from ethanol gave pale yellow prisms, m. p. 153—154° (Found: C, 37·4; H, 2·1; Br, 38·55. $C_{13}H_8O_4N_2Br_2$ requires C, 37·5; H, 1·9; Br, 38·4%).

(*b*) *Chlorination.* A solution of the dinitro-compound (2·58 g.) and silver sulphate (3·12 g.) in concentrated sulphuric acid (50 c.c.) was shaken with an excess of chlorine. After 5 hr. pressure ceased to fall and recovery of silver chloride was quantitative. The crude product, m. p. 112—113°, obtained on dilution of the filtered solution was recrystallised seven times from acetic acid, giving *di-*(2-*chloro*-4-*nitrophenyl*)*methane* (50—60%) in pale yellow prisms, m. p. 124—125° (Found: N, 8·6; Cl, 21·7. $C_{13}H_8O_4N_2Cl_2$ requires N, 9·0; Cl, 21·7%).

Reduction of Di-(2-*halogeno*-4-*nitrophenyl*)*methanes.*—(*a*) The dibromo-compound (4·85 g.) was reduced with iron and acetic acid (70 c.c.), and the product treated with acetic anhydride to give *di-*(4-*acetamido*-2-*bromophenyl*)*methane* (4·48 g.) which after crystallisation from ethanol had m. p. 236° and 243° (dimorphic) (Found: C, 46·3; H, 3·9; Br, 36·5. $C_{17}H_{16}O_2N_2Br_2$ requires C, 46·4; H, 3·7; Br, 36·3%). Hydrolysis with 50% sulphuric acid followed by crystallisation from petroleum (b. p. 90—120°) and from aqueous ethanol gave *di-*(4-*amino*-2-*bromophenyl*)*methane*, m. p. 109—110° and 129—130° (dimorphic forms) (Found: C, 43·85; H, 3·9; Br, 44·65. $C_{13}H_{12}N_2Br_2$ requires C, 43·85; H, 3·4; Br, 44·9%).

(*b*) Powdered dichloro-compound (1·42 g.) was washed with ethanol into a hot solution of stannous chloride (9 g.) in concentrated hydrochloric acid (30 c.c.). *Di-*(4-*amino*-2-*chlorophenyl*)-*methane* (1·2 g.) was obtained on basifying the clear solution: it separated from aqueous ethanol as a crystalline powder, m. p. 102·5—103·5° (Found: C, 58·5; H, 4·4; Cl, 26·6. $C_{13}H_{12}N_2Cl_2$ requires C, 58·4; H, 4·5; Cl, 26·55%). *Di-*(4-*acetamido*-2-*chlorophenyl*)*methane* crystallised from aqueous ethanol in fine needles, m. p. 226—227° (Found: N, 8·0; Cl, 20·1. $C_{17}H_{16}O_2N_2Cl_2$ requires N, 8·0; Cl, 20·2%). The low m. p. form encountered in previously described specimens of slightly lesser purity could not be detected in the highly purified compound (cf. *J.*, 1950, 407).

*Bromination of Di-*p*-nitrophenylmethane in Organic Solvents.*—(*a*) The dinitro-compound (3·55 g.) was gently refluxed with bromine (4·8 g., 2·2 mols.) in carbon tetrachloride (100 c.c.) containing iodine (0·05 g.) for 7 days with almost complete exclusion of light. The solvent, which still contained bromine, was evaporated and the residue warmed with methanol. The crystals (3·5 g.; m. p. *ca.* 100°) obtained on cooling gave unchanged dinitro-compound (0·77 g., 22%) when recrystallised from acetic acid. Dilution of combined mother-liquor and crystallisation of the precipitate from acetic acid or methanol gave di-*p*-nitrophenylmethyl bromide (1·9 g., 41%) in pale yellow prisms, m. p. 97—98° (Found: C, 46·5; H, 3·0; Br, 23·2. Calc. for $C_{13}H_9O_4N_2Br$: C, 46·3; H, 2·7; Br, 23·7%). Orazi and Giunti (*loc. cit.*) recorded m. p. 98—98·5°.

(*b*) The reaction mixture described in (*a*), but without addition of iodine, was refluxed under illumination (incandescent lamp, 200 w) until the bromine had largely reacted (<2 hr.). Crystallisation of the product from acetic acid gave *dibromodi-*p-*nitrophenylmethane* (3·1 g., 54%) in pale yellow prisms, m. p. 168—169° (Found: C, 37·6; H, 1·8; Br, 38·5. $C_{13}H_8O_4N_2Br_2$ requires C, 37·5; H, 1·9; Br, 38·4%). When refluxed in acetic acid for 15 hr. this compound was converted into 4 : 4′-dinitrobenzophenone. The same product resulted when the pale yellow solution formed by the dibromide in concentrated sulphuric acid was poured on ice.

(*c*) The dinitro-compound (7·1 g.) was gently refluxed with bromine (4·8 g., 1·1 mol.) in carbon tetrachloride (150 c.c.) under illumination (200 w) for 30 minutes. On removal of the solvent and crystallisation of the residue from acetic acid it was possible to recover (preferably with

seeding) crops of unchanged material and of dibromodi-*p*-nitrophenylmethane (on one occasion 1·6 g., 14%) and ultimately of di-*p*-nitrophenylmethyl bromide (35—40%).

(*d*) When the dinitro-compound (7·1 g.) was refluxed with excess of bromine in acetic acid (140 c.c.) containing iodine (0·1 g.) the only product isolated after 90 hr. was 4 : 4′-dinitrobenzophenone (6·2 g., 84%). After 15 hr., however, di-*p*-nitrophenylmethyl bromide was isolated in *ca.* 10% yield.

*Behaviour of Di-*p*-nitrophenylmethyl Bromide in Sulphuric Acid.*—(*a*) The powdered dinitro-compound readily formed a pale yellow solution in the concentrated acid and was regenerated essentially unchanged when poured into water.

(*b*) To a solution of the dinitro-compound (2·84 g.) in concentrated sulphuric acid (20 c.c.) was added silver sulphate (1·6 g.) in the same solvent (10 c.c.); silver bromide was precipitated immediately. The mixture was added to ice and filtered after 1 hr. The filtrate was boiled gently until crystals appeared, filtered, and heated further to ensure maximum recovery of hydrolysis product. The crystals (1·7 g., 74%) melted at 169° (rapid heating) followed by solidification of the melt and further melting at *ca.* 280° (with slow heating there was no lower m. p.). Crystallisation from aqueous acetic acid gave di-*p*-nitrophenylmethanol in platelets, m. p. 169—170° (no change after raising bath temperature to 280°, cooling and redetermining m. p.) (Found: C, 57·3; H, 3·7; N, 10·0. Calc. for $C_{13}H_{10}O_5N_2$: C, 56·9; H, 3·7; N, 10·2%). Curtin and Leskowitz (*loc. cit.*) found m. p. 168—169° for this alcohol.

When the original sulphuric acid solution was filtered through sintered glass to remove the silver bromide and poured into water instead of on ice, some of the alcohol was precipitated. If the filtrate was then basified with sodium hydroxide a deep orange-red colour developed, evidently due to the anion of the sulphonated alcohol. This solution slowly and continuously deposited 4 : 4′-dinitrobenzophenone with progressive fading of the colour. In the same way the pale bronze-coloured solution of di-*p*-nitrophenylmethanol (0·07 g.) in methanol containing sodium methoxide (from 0·01 g. of sodium) slowly deposited 4 : 4′-dinitrobenzophenone and was fully oxidised within 42 hr.

(*c*) A solution of the dinitro-compound (1·34 g.) in sulphuric acid was treated as in (*b*) and the silver bromide recovered (quantitative). The filtrate was diluted with water, with shaking, so that considerable heat was generated. The resultant precipitate (0·98 g.) was removed, dried at 50°, and boiled with acetic acid. Filtration of the cool suspension gave bisdi-*p*-nitrophenylmethyl ether (0·26 g., 25%), which when crystallised from acetic acid (extractor) had m. p. 284—286° (Found: C, 59·05; H, 3·5. Calc. for $C_{26}H_{18}O_9N_4$: C, 58·9; H, 3·4%) (Curtin and Leskowitz, *loc. cit.*, gave m. p. 286—287°). On dilution with water the acetic acid filtrate gave di-*p*-nitrophenylmethanol (0·65 g., 60%), m. p. 169—170°.

The ether (m. p. 284—286° from acetic acid) was also obtained by heating the crude methanol from (*b*), m. p. 169° and *ca.* 280°, for several minutes at 180—200°.

*Di-*p*-nitrophenylmethyl Acetate.*—(*a*) Di-*p*-nitrophenylmethyl bromide (0·33 g.) was added to a suspension of silver acetate (1·8 g.) in acetic acid (15 c.c.), which was refluxed for 5 min., filtered, and diluted with water. The *acetate* (0·32 g.) formed crystals, m. p. 175—176°, from acetic acid (Found: C, 57·2; H, 3·8; N, 8·9. $C_{15}H_{12}O_6N_2$ requires C, 56·95; H, 3·8; N, 8·9%). The same compound was formed, with some side-product of high m. p., when the bromide was refluxed with potassium acetate in acetic acid.

(*b*) Di-*p*-nitrophenylmethanol remained unchanged after 65 hr. in acetic acid solution at 20° and after 2 hr. at 100°. It was partly acetylated after 5 min. in boiling acetic anhydride but on addition of a trace of sulphuric acid it reacted completely to give the acetate, m. p. 175—176°.

The acetate was hydrolysed to the alcohol when refluxed in methanol (30 c.c.) in presence of sulphuric acid (1 c.c.). Its alcoholic solution developed a violet colour on addition of potassium hydroxide; the colour gradually faded with deposition of 4 : 4′-dinitrobenzophenone.

*Action of Sulphuric Acid on Di-*p*-nitrophenylmethanol and its Derivatives.*—The alcohol dissolved in concentrated sulphuric acid to a pale yellow solution which gave only a slight amorphous precipitate when added to ice: after centrifugation the solution remained clear for 3½ days at 0° in presence of a crystal of the alcohol. A portion of the solution regenerated the alcohol on gentle boiling: another portion, basified with potassium hydroxide, gave a deep orange-red solution which deposited 4 : 4′-dinitrobenzophenone.

When a sulphuric acid solution of the alcohol was quickly diluted with water the precipitate which formed consisted of regenerated alcohol in admixture with a lesser quantity of the ether.

Both the acetate and the ether formed pale yellow solutions in sulphuric acid. The clear solutions obtained on addition to ice regenerated the alcohol when heated.

Action of Oleum and Chlorosulphonic Acid on Di-p-nitrophenylmethyl Derivatives.—Equivalent quantities (0·002 mol.) of di-*p*-nitrophenylmethane, di-*p*-nitrophenylmethyl bromide, and di-*p*-nitrophenylmethanol were dissolved separately in concentrated sulphuric acid (3 c.c.), in oleum (20% w/w free SO_3) (3 c.c.), and in chlorosulphonic acid (3 c.c.). The three solutions in sulphuric acid were pale yellow and almost identical in appearance: the six solutions in oleum and chlorosulphonic acid were bright yellow and almost identical in appearance. After 1 hr., during which time there was no appreciable colour change, the solutions were added to ice. Di-*p*-nitrophenylmethane was in each case recovered unchanged. Di-*p*-nitrophenylmethyl bromide, unchanged by sulphuric acid, had been converted in oleum into the hydrogen sulphate: on boiling the clear solution the alcohol was regenerated. The alcohol had also been sulphonated by oleum. The products from chlorosulphonic acid were not further examined.

Dismutation of Bisdi-p-nitrophenylmethyl Ether.—A specimen of the ether (0·17 g.), which had been crystallised from acetic acid, was heated to 290°/0·2 mm. with a view to sublimation. The sublimate (0·14 g.) was a mixture, m. p. 150—153°, readily separated by the use of Girard reagent T into di-*p*-nitrophenylmethane (0·05 g.) and 4 : 4′-dinitrobenzophenone (0·04 g.). These products on crystallisation from acetic acid had m. p.s 186—187° and 191—192°, respectively, not depressed by authentic specimens (Hunsberger and Amstutz, *J. Amer. Chem. Soc.*, 1949, **71**, 2638, record m. p.s 188·6—189·4° and 189·6—190·6°, whereas the older literature gives m. p.s 183° and 189° respectively).

A specimen of the ether which had been recrystallised twice from alcoholic pyridine behaved similarly when heated to 290°.

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Interaction between Polynitro-compounds and Aromatic Hydrocarbons and Bases. Part XIV. Stabilities of Some Solid Complexes of Trinitrobenzene and Trinitrotoluene.*

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The relative stabilities of some solid complexes of 1 : 3 : 5-trinitrobenzene and of 2 : 4 : 6-trinitrotoluene with various aromatic hydrocarbons have been investigated by measuring the concentration of trinitrobenzene or trinitrotoluene in aqueous solution in equilibrium with the complex. Values of the free energy of formation of the complexes from their parent solids are derived.

THE equilibrium concentration of picric acid obtained when solid naphthalene picrate and other hydrocarbon picrates are shaken with excess of hydrocarbon in water has been used as a measure of the stability of the solid hydrocarbon picrates (Behrend, *Z. physikal. Chem.*, 1894, **15**, 183; Brönsted, *ibid.*, 1911, **78**, 284; Dimroth and Bamberger, *Annalen*, 1924, **438**, 67; Bell and Fendley, *Trans. Faraday Soc.*, 1949, **45**, 121). Values of the free energy of formation of naphthalene picrate obtained from measurements by Brönsted (*loc. cit.*) and by Bell and Fendley (*loc. cit.*) are in agreement with cryoscopic measurements (Brown, *J.*, 1925, **127**, 345). In the analogous systems of the trinitrobenzene and trinitrotoluene complexes the concentrations of trinitrobenzene (TNB) and of trinitrotoluene (TNT) so obtained are very much less than in the case of picric acid, but correspond in the same way to the stabilities of the hydrocarbon–polynitro-compound complexes, the more stable complex giving rise to the smaller concentration of TNB or TNT in solution.

EXPERIMENTAL

Materials.—The hydrocarbons were obtained from laboratory sources and were purified by recrystallization from ethanol. We are indebted to Dr. J. K. Marsh for a specimen of spectroscopically pure anthracene. 1 : 3 : 5-Trinitrobenzene was obtained as pale cream-coloured

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rhombs by recrystallization from ethanol [m. p. 121° (corr.)]; 2 : 4 : 6-trinitrotoluene was recrystallized from ethanol [m. p. 82° (corr.)]. Complexes were made by mixing hot solutions of the components and allowing them to cool. The m. p.s of the complexes so prepared agree with accepted values, where these are known.

Estimation of Trinitrobenzene.—Lobry de Bruyn and van Leent (*Rec. Trav. chim.*, **1895**, **14**, 150) found that solutions of trinitrobenzene gave with strong alkali an orange-red colour, and this has been used as a basis for its colorimetric estimation in aqueous solution. The concentration of an unknown solution was determined by adding to it an equal volume of N-potassium hydroxide and comparing the colour so produced with the colour developed by a standard solution of trinitrobenzene of similar concentration treated in the same way. The colours were compared in a DuBosq colorimeter. The colours so produced are liable to slow fading, but by preparing coloured solutions from the unknown and the known solutions simultaneously the effect of fading was eliminated and reproducible estimations obtained.

Estimation of Trinitrotoluene.—2-Diethylaminoethanol in the presence of acetone develops a colour with aqueous solutions of trinitrotoluene (Golding and Rushman, *J. Ind. Hyg.*, **1943**, **25**, 164). The concentration of an unknown solution was determined by adding to it an equal volume of a solution of diethylaminoethanol (5 g.) in acetone (100 c.c.) and comparing (DuBosq) the colour so produced with that developed by a standard solution of trinitrotoluene of similar concentration treated in the same way. When the aqueous trinitrotoluene and the reagent solution are first mixed, a purple colour is produced, which changes in about 10 min. to a red colour. This persists for 24 hr., but the comparison of the colours of the unknown and the standard solution was made 30 min. after the solutions were mixed.

Procedure.—A complex (*ca.* 0·2 g.) and its parent hydrocarbon (*ca.* 0·2 g.) were sealed into an ampoule containing distilled water (*ca.* 15 c.c.). Ampoules were rotated end-over-end in a thermostat at 25·0° until the solutions attained equilibrium; as this process was slow, measurements on a given system were repeated at intervals of about a week until consistent results were obtained; their consistency and reproducibility indicate that true equilibria were in fact established. The aqueous solution (5 c.c.) was removed from the ampoule by suction through a glass-wool filter, and either suitably diluted or used direct in the colorimetric estimation. The solubility of trinitro-benzene and -toluene was measured analogously.

Results and Discussion

The results are collected in the Table in order of increasing stability of the trinitrobenzene complex. The order of stability follows directly from the decreasing concentrations

Stabilities of solid polynitro-compound–hydrocarbon complexes at 25·0°.

	1 : 1 TNB Complexes			1 : 1 TNT Complexes		
Parent hydrocarbon	M. p.	c_2	$\Delta G°$	M. p.	c_2	$\Delta G°$
Anthracene	162°	0·100	−0·84	(*a*) 159°	0·107	−0·14
Durene	101	0·099	−0·84	(*b*)		
Fluorene	105	0·091	−0·89	89	0·034	−0·83
Hexamethylbenzene	173	0·043	−1·34	(*c*) 123	0·085	−0·28
Pentamethylbenzene	119	0·0279	−1·59	(*c*) 81	0·045	−0·66
Acenaphthene		(*d*)		111	0·0151	−1·30
Naphthalene	152	0·0114	−2·08	97	0·0123	−1·43
Phenanthrene	164	0·0070	−2·41	102	0·0142	−1·34
2-Methylnaphthalene	123	0·0062	−2·48	(*c*) 74	0·0079	−1·69
Fluoranthene	204	0·0030	−2·91	132	0·0096	−1·57
1 : 3 : 5-Trinitrobenzene		c_1 = 0·404 (*e*)				
2 : 4 : 6-Trinitrotoluene					c_1 = 0·135 (*f*)	

(*a*) Incongruent m. p. (*b*) Durene–TNT complex is not stable. (*c*) These substances have not been previously reported, but they have not been fully characterised in this work. (*d*) Equilibrium was not attained in this system. (*e*) Lobry de Bruyn and van Leent (*loc. cit.*) report 0·40 g./l. (*f*) Taylor and Rinkenbach (*J. Amer. Chem. Soc.*, **1923**, **45**, 47) report 0·120 g./l. at 20·0°.

of nitro-compound (c_2, g./l.). Values of the free energy of formation ($\Delta G°$, kcal./mole) are determined from the relation $\Delta G° = RT \ln c_2/c_1$, where c_1 (g./l.) is the solubility of the nitro-compound and c_2 is the concentration thereof in equilibrium with solid complex and solid hydrocarbon. The assumption is made that the solutions are sufficiently dilute for activities to be proportional to concentrations.

Dimroth and Bamberger (*loc. cit.*) found a similar sequence for the stabilities of solid

hydrocarbon picrates at 24·1°, *viz.*, benzene<fluorene<anthracene<indene<naphthalene<1-<2-methylnaphthalene. Bell and Fendley (*loc. cit.*) found for naphthalene picrate $\Delta G^\circ = -2{\cdot}075$ kcal./mole, which is very close to the value (−2·08) found here for the naphthalene–trinitrobenzene complex. This leads to the conclusion that there is no very great difference in the stability of the solid picrates and the corresponding trinitrobenzene derivatives, while the trinitrotoluene derivatives are rather less stable (naphthalene TNT, $\Delta G^\circ = -1{\cdot}43$ kcal./mole).

The free energies of formation obtained by this method refer to the reaction $M_{cryst.} + N_{cryst.} = MN_{cryst.}$ and are therefore distinct from the free energies of formation (or equilibrium constants) determined by various methods involving equilibrium in solution, as these depend on the interaction of the species in solution with the solvent molecules. Nevertheless certain parallels can be found. Moore, Shepherd, and Goodall (*J.*, 1931, 1447) found naphthalene picrate less stable than 2-methylnaphthalene picrate, and Anderson and Hammick (*J.*, 1950, 1089) found durene picrate less stable than hexamethylbenzene picrate. These relative stabilities are paralleled in both the trinitrobenzene and the trinitrotoluene derivatives in the solid state.

The facts that the order of the stabilities is broadly similar for the three series of nitrocompounds, and that the values of the free energy of formation of the three derivatives of naphthalene are of the same order of magnitude, indicate that the same sort of molecular interaction is operative in all cases. Individual discrepancies, *e.g.*, the near equality of the stabilities of the trinitrobenzene and the trinitrotoluene derivatives of fluorene, or the inversion of the relative stabilities of naphthalene and phenanthrene in the two series here examined may be attributable to differences of packing of the molecules in the crystals.

We are indebted to the Ministry of Education for a grant (to H. P. H.) under the Further Education and Training Scheme during part of the tenure of which this work was carried out.

The Dyson Perrins Laboratory, Oxford.
The Chemical Laboratory, Trinity College, Dublin. [*Received, September 14th*, 1954.]

The Direct Hydroxylation of 6-*Phenyl*meso*benzanthrone and Two Benzo-derivatives of* meso*Benzanthrone, and Some Related Reactions.*

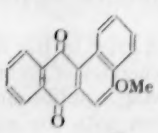
By Alan J. Backhouse, William Bradley, and F. K. Sutcliffe.

[Reprint Order No. 5756.]

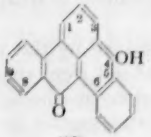
In continuation of earlier work the constitution assigned to the product of direct hydroxylation of 5 : 6-benzo*meso*benzanthrone has been confirmed. Under the same conditions 8 : 9-benzo*meso*benzanthrone affords a *mono*-hydroxy-derivative, the constitution of which has been established. 6-Phenyl*meso*benzanthrone affords the 4-hydroxy-derivative with potassium hydroxide and the 4-anilino-derivative with sodioaniline. 3-Bromo*meso*-benzanthrone yields the 6-phenyl derivative with phenylmagnesium bromide, an example of the rule that nuclear substitution is the predominant reaction when the reacting anion is highly active.

In a previous communication (Bradley and Sutcliffe, *J.*, 1952, 1247) it was shown that 5 : 6-benzo*meso*benzanthrone gave a monohydroxy-derivative on being heated at 110° with alcoholic potassium hydroxide, and that 8 : 9-benzo*meso*benzanthrone gave a small amount of an alkali-soluble derivative with potassium hydroxide at 220—230°. The first was considered to be 4-hydroxy-5 : 6-benzo*meso*benzanthrone (II), and the correctness of this has now been shown by a synthesis from 3-methoxy-1 : 2-benzanthraquinone (I), glycerol, and sulphuric acid, the *O*-methyl substituent being eliminated. The experiments with 8 : 9-benzo*meso*benzanthrone have been extended. The addition of manganese dioxide to the alkali melt results in an increased yield of the alkali-soluble derivative from which a monohydroxy-8 : 9-benzo*meso*benzanthrone has now been isolated. The new derivative

gives a monomethyl ether, but it does not form a boroacetate with Dimroth's reagent. In this, as in colour, the green fluorescence of its solution in aqueous alkalis, and the absorption spectrum of its solution in alcohol, it closely resembles 4-hydroxy*meso*benzanthrone, and the analogous constitution (III) is indicated. 4-Methoxy-8 : 9-benzo*meso*benzanthrone yields (III) on fusion with potassium hydroxide, and heating (III) with aqueous ammonia



(I)



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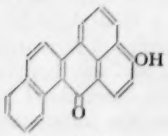
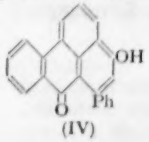


(III)

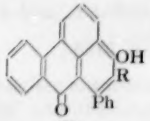
gives 4-amino-8 : 9-benzo*meso*benzanthrone (III; NH_2 for OH). There was no evidence of the formation of a violanthrone derivative in the action of potassium hydroxide on the *O*-methyl derivative, and this supports the constitution assigned.

Fusion of 6-phenyl*meso*benzanthrone with potassium hydroxide and manganese dioxide gave 4-hydroxy-6-phenyl*meso*benzanthrone (IV) and 6 : 9-diphenylviolanthrone. In the absence of manganese dioxide the yield of the hydroxy-compound was lower and that of diphenylviolanthrone higher. From (IV) were derived the *O*-methyl ether (IV; OMe for OH), 4-hydroxy-6-phenyl-5-phenylazo*meso*benzanthrone (V; R = PhN_2), 5-amino-4-hydroxy-6-phenyl*meso*benzanthrone (V; R = NH_2), and the oxazole (VI). 6-Phenyl-*meso*benzanthrone and sodioaniline gave 4-anilino-6-phenyl*meso*benzanthrone (IV; NHPh for OH), hydrolysed to (IV) by hot potassium hydroxide. There was no indication of the formation of a derivative of 4 : 4'-di*meso*benzanthronyl in this reaction. In contrast *meso*-benzanthrone itself yields 4 : 4'-di*meso*benzanthronyl as the main product, and 4-anilino-*meso*benzanthrone is formed only in minor amount (Lüttringhaus and Neresheimer, *Annalen*, 1929, **473**, 275).

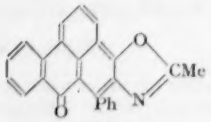
Treatment of 3-bromo*meso*benzanthrone with phenylmagnesium bromide gave 3-bromo-6-phenyl*meso*benzanthrone (VII), an instance of nuclear substitution by an anion, without replacement of halogen. The constitution of this compound was proved by debromination to 6-phenyl*meso*benzanthrone by Busch, Wiher, and Zink's method (*J. prakt. Chem.*, 1940, **155**, 163). Heating (VII) with alcoholic potassium hydroxide gave 6 : 13-diphenyl*iso*violanthrone.



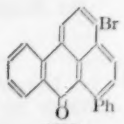
(IV)



(V)



(VI)



(VII)

The occurrence of nuclear substitution when the reagent is the active anion of the Grignard reagent, and of self-coupling when it is the less active hydroxyl ion, is a further instance of the relation between substitution and self-coupling processes discussed by Bradley and Sutcliffe (*J.*, 1954, 708).

The formation of *mono*hydroxy-derivatives of the *mono*ketones, 5 : 6- and 8 : 9-benzo-*meso*benzanthrone and 6-phenyl*meso*benzanthrone, on fusion with an alkali hydroxide, supports the conclusion (Bradley and Sutcliffe, *J.*, 1951, 2118) that the number of hydroxyl groups introduced equals the number of activating carbonyl groups present.

Experimental

*Action of Potassium Hydroxide on 6-Phenyl*meso*benzanthrone.*—6-Phenyl*meso*benzanthrone was prepared by Allen and Overbaugh's method (*J. Amer. Chem. Soc.*, 1935, **57**, 740); the purified product had m. p. 185—186°, as recorded.

*4-Hydroxy-6-phenyl*meso*benzanthrone.*—An intimate mixture of 6-phenyl*meso*benzanthrone (10 g.) and manganese dioxide (10 g.) was added during 0·5 hr. to a stirred melt of potassium

hydroxide (100 g.) and potassium acetate (10 g.) at 220°, and then the temperature was raised to 240° for 1 hr. The product was cooled and added to water (1·5 l.) and the resulting suspension was filtered. The residue was extracted with water and the combined alkaline solutions were acidified. The precipitate which formed was collected, washed, dried, and crystallised from chlorobenzene; it afforded 7·5 g. of yellow crystals, m. p. 274—276° (Found: C, 85·3; H, 4·3. $C_{23}H_{14}O_2$ requires C, 85·7; H, 4·4%). 4-*Hydroxy*-6-*phenyl*meso*benzanthrone* gave a yellow solution in aqueous sodium hydroxide, and a deep yellow solution with a slight greenish-yellow fluorescence in concentrated sulphuric acid. There was no colour change in acetic anhydride on the addition of boroacetic anhydride.

6 : 9-*Diphenylviolanthrone*.—The alkali-insoluble material obtained in the above preparation was heated with acidified sodium sulphite solution to remove manganese dioxide, then collected, washed, dried, dissolved in hot trichlorobenzene, and chromatographed at 150° on alumina using a jacketed column. A blue zone formed and this was extracted with trichlorobenzene. Concentration of the extract gave 1 g. of blue-violet needles which did not melt below 400° or dissolve in aqueous alkaline sodium dithionite. They dissolved in pyridine with a deep bluish-violet colour, changed to bluish-red on the addition of aqueous alkaline sodium dithionite. The light absorption of a solution of the product in concentrated sulphuric acid ($\lambda_{max.}$ at 390, 530, 570, 740, 790, and 870 mμ) resembled that of violanthrone ($\lambda_{max.}$ at 390, 570, 760, and 850 mμ).

When manganese dioxide was omitted from the reactants in the above preparation the yield of 4-hydroxy-6-phenyl*meso*benzanthrone, m. p. 274—276°, was 0·65 g., and that of 6 : 9-diphenylviolanthrone was 3·5 g.

4-*Methoxy*-6-*phenyl*meso*benzanthrone*.—4-Hydroxy-6-phenyl*meso*benzanthrone (2 g.) was refluxed for 4 hr. with methyl toluene-*p*-sulphonate (2 g.) and potassium carbonate (2 g.) in chlorobenzene (100 c.c.). The resulting suspension was filtered, and the cooled filtrate was washed with aqueous sodium hydroxide, then with water, and finally concentrated. Greenish-yellow needles (2 g.) separated which, after crystallisation from ethanol, had m. p. 175—176° (Found: C, 85·5; H, 4·7; OMe, 9·2. $C_{23}H_{13}O{\cdot}OMe$ requires, C, 85·7; H, 4·8; OMe, 9·2%). In concentrated sulphuric acid 4-*methoxy*-6-*phenyl*meso*benzanthrone* gave a deep yellow solution with a faint greenish-yellow fluorescence. It was recovered unaltered after 4 hours' refluxing with acetic anhydride.

4-*Acetoxy*-6-*phenyl*meso*benzanthrone* resulted (0·9 g.) when the 4-hydroxy-derivative (1 g.) was refluxed with acetic anhydride for 3 hr. It separated from alcohol in greenish-yellow crystals, m. p. 187—189° (Found: C, 81·8; H, 4·5. $C_{25}H_{16}O_3$ requires C, 82·4; H, 4·4%).

4-*Hydroxy*-6-*phenyl*-5-*phenylazo*meso*benzanthrone* was obtained when aniline (0·93 g.) was diazotized in hydrochloric acid, and the resulting solution was added slowly and below 8° to a stirred solution of 4-hydroxy-6-phenyl*meso*benzanthrone (3·22 g.) in water (20 c.c.) containing sodium hydroxide (0·5 g.) and sodium carbonate (2·5 g.). The red precipitate of 4-*hydroxy*-6-*phenyl*-5-*phenylazo*meso*benzanthrone* which formed was collected after 1 hr., dried, and purified from alcohol. Red crystals (3 g.), m. p. 226—228° (Found: C, 81·4; H, 4·3; N, 6·5. $C_{29}H_{18}O_2N_2$ requires C, 81·6; H, 4·3; N, 6·7%), were obtained.

2′-*Methyl*-6-*phenyloxazolo*(5′ : 4′-4 : 5)meso*benzanthrone* (VI).—The above azo-compound (2 g.) was dissolved in ethanol (150 c.c.), sodium dithionite (5 g.) was added, and then water at such a rate that none of the azo-compound was precipitated. The colour changed from bluish-red to orange. After 1 hour's refluxing the resulting solution was cooled, then acidified with acetic acid, and finally extracted continuously with benzene. The concentrated extract afforded 1 g. of red-brown crystals, m. p. 185—188°. A portion of the product (0·5 g.) was refluxed for 1 hr. with an excess of acetic anhydride. The yellow solution which formed was concentrated and cooled. It gave yellow crystals, which after purification from ethanol were obtained as fine needles (0·4 g.), m. p. 279—280° (Found: C, 82·6; H, 4·2; N, 4·2. $C_{25}H_{15}O_2N$ requires C, 83·0; H, 4·2; N, 3·9%). 2′-*Methyl*-6-*phenyloxazolo*(5′ : 4′-4 : 5)meso*benzanthrone* was insoluble in aqueous acid or alkali. It was unaffected by prolonged refluxing with methanolic potassium hydroxide.

3-*Bromo*-6-*phenyl*meso*benzanthrone*.—3-Bromo*meso*benzanthrone (100 g.) was added during 30 min. to a stirred solution of the Grignard reagent prepared from bromobenzene (150 g.), magnesium (25 g.), and ether (700 c.c.). Stirring was continued for 5 hr. and then 30% acetic acid (370 c.c.) was added. After distillation in steam the residual aqueous solution was separated from a solid, and this was dried, dissolved in benzene (350 c.c.), and kept at 0° for several days. A solid separated and this was crystallised three times from benzene (charcoal). 3-*Bromo*-6-*phenyl*meso*benzanthrone* (25·5 g.) forms yellow crystals, m. p. 202—203° (Found: C, 71·3; H, 3·3; Br, 21·3. $C_{23}H_{13}OBr$ requires C, 71·7; H, 3·4; Br, 20·8%).

Debromination. Palladium chloride (0·18 g.) was dissolved in water (10 c.c.) and added with vigorous stirring to a suspension of calcium carbonate (10 g.) in water (10 c.c.). The resulting pale brown precipitate was collected, washed, and dried. A portion (2 g.) of the catalyst so prepared was heated in a sealed tube at 140—145° for 1·5 hr. with 3-bromo-6-phenyl*meso*benzanthrone (3 g.), methanol (50 c.c.), and 100% hydrazine hydrate (1·4 c.c.). The product was stirred with an excess of hydrochloric acid, and the solid collected, dried, and chromatographed on alumina from chlorobenzene at 100° using a jacketed column. Two bands formed. The more strongly adsorbed was blue; elution with chlorobenzene gave 6 : 9-diphenylvioloanthrone (1·3 g.) having the same absorption spectrum in concentrated sulphuric acid as the same compound prepared by heating 6-phenyl*meso*benzanthrone with potassium hydroxide. The less strongly absorbed was yellow; elution with chlorobenzene gave 6-phenyl*meso*benzanthrone (0·5 g.; m. p. 186—188°) identical (mixed m. p.) with the compound prepared from *meso*benzanthrone and phenylmagnesium bromide.

6 : 13-*Diphenylisoviolanthrone.*—3-Bromo-6-phenyl*meso*benzanthrone (5 g.) was added during 10 min. at 150° to a stirred melt of potassium hydroxide (48 g.) in ethanol (30 g.). After 2 hours' stirring the product was cooled and added to water (1 l.), and the resulting suspension was filtered. The residue, after being washed until neutral, was dried, and recrystallised from trichlorobenzene. Violet needles (2·5 g.) which did not melt below 400° were obtained. They dissolved in pyridine forming a violet solution which changed to blue on the addition of aqueous alkaline sodium dithionite. The absorption spectrum of the compound in concentrated sulphuric acid, like that of *iso*violanthrone, exhibited light absorption maxima at 390 and 735 mμ. Presence of some of a violanthrone derivative was not excluded.

4-*Anilino-6-phenyl*meso*benzanthrone.*—A solution of sodioaniline was prepared from aniline (75 g.), sodium (3 g.), copper bronze (0·1 g.), and nickel oxide (0·1 g.). 6-Phenyl*meso*benzanthrone was added at 40—45° to the solution which was stirred for 2 hr., then cooled, and added to 5% hydrochloric acid (1 l.). The precipitate was collected, extracted with hot dilute hydrochloric acid, washed, dried, and purified from chlorobenzene. 4-*Anilino-6-phenyl*meso*benzanthrone* crystallised in red needles (4 g.), m. p. 264—265° (Found : C, 87·7; H, 4·5; N, 3·9. $C_{29}H_{19}ON$ requires C, 87·7; H, 4·8; N, 3·5%). There was no indication of the formation of 6 : 6′-diphenyldi-(4-*meso*benzanthronyl) in the reaction of 6-phenyl*meso*benzanthrone with sodioaniline.

Hydrolysis. 4-Anilino-6-phenyl*meso*benzanthrone (0·5 g.) was heated in a sealed tube at 250° for 5 hr. with potassium hydroxide (5 g.) and water (10 c.c.). After addition to water, the precipitated solid was collected and washed with dilute sodium hydroxide, and the combined alkaline solutions were acidified with hydrochloric acid. A yellow precipitate formed which, after purification from chlorobenzene, afforded yellow crystals (0·3 g.), m. p. 274—276°, not depressed on admixture with 4-hydroxy-6-phenyl*meso*benzanthrone prepared from 6-phenyl-*meso*benzanthrone and potassium hydroxide.

4-*Hydroxy-5* : 6-*benzo*meso*benzanthrone.* (II).—A mixture of 3-methoxy-1 : 2-benzanthraquinone (1 g.), glycerol (1 g.), aniline sulphate (1 g.), concentrated sulphuric acid (13·5 c.c.), and water (3·9 c.c.) was stirred and heated at 140° for 1·25 hr. The resulting solution was cooled and added to water, and the dark brown precipitate was collected and washed (0·95 g.). It dissolved almost completely in dilute sodium hydroxide solution with a pink colour and a yellow fluorescence. The filtered solution was acidified, and the resulting precipitate was washed, dried, and crystallised from nitrobenzene. Light brown needles, m. p. 322—324°, were obtained, the m. p. of which was not depressed on admixture with the hydroxy-compound, m. p. 324—326°, prepared by the action of ethanolic potassium hydroxide on 5 : 6-benzo*meso*benzanthrone. Acetylation of the material, m. p. 322—324°, with hot acetic anhydride and pyridine, and crystallisation of the product from acetic acid gave pale yellow needles, m. p. 276—278° (decomp.), not depressed on mixing with the acetyl derivative, m. p. 280—281° (decomp.), of the hydroxy-compound, m. p. 324—326°.

4-*Hydroxy-8* : 9-*benzo*meso*benzanthrone.*—8 : 9-Benzo*meso*benzanthrone was prepared by the method of Scholl (G.P. 239,671) and Cook (*J.*, 1939, 268). After distillation at 210—230°/10^{-4} mm. and subsequent crystallisation from toluene it was obtained as bright orange-yellow needles, m. p. 184—188°. An intimate mixture of the ketone (3 g.) and manganese dioxide (3 g.) was added during 10 min. at 210° to potassium hydroxide (30 g.) and potassium acetate (3 g.). The melt was then stirred for 1 hr. at 240°, during which it became grey-brown and viscous. After cooling and addition to water (600 c.c.), the resulting suspension was filtered, and the dark reddish-yellow filtrate, which exhibited a very strong green fluorescence, was acidified with hydrochloric acid. The precipitate which formed was collected, washed, and dried (1·35 g.).

Sublimation at 250° *in vacuo* gave a single band of bright yellow needles, m. p. 302—304° (Found : C, 84·9; H, 4·2. $C_{21}H_{12}O_2$ requires C, 85·2; H, 4·1%). *4-Hydroxy-8 : 9-benzo*mes*obenzanthrone* gave a yellow solution in acetic anhydride, unchanged on the addition of boroacetic anhydride. It gave a yellow solution and a green fluorescence in concentrated sulphuric acid.

*4-Methoxy-8 : 9-benzo*mes*obenzanthrone.*—The 4-hydroxy-derivative (0·3 g.), methyl toluene-*p*-sulphonate (0·6 g.), and potassium carbonate (0·6 g.) were refluxed 5 hr. in chlorobenzene (50 c.c.). The resulting suspension was filtered, and the cooled filtrate washed with dilute sodium hydroxide, then water, and chromatographed on alumina. A yellow band formed and this was extracted with chlorobenzene. Concentration gave yellow crystals of *4-methoxy-8 : 9-benzo*mes*obenzanthrone* (0·17 g.), m. p. 199—201° (Found : OMe, 12·0. $C_{21}H_{11}O{\cdot}OMe$ requires OMe, 10·5%).

Hydrolysis. 4-Methoxy-8 : 9-benz*omeso*benzanthrone (0·1 g.) was stirred for 1 hr. at 240° with potassium hydroxide (1 g.) and potassium acetate (0·1 g.). On addition to water (150 c.c.) a yellow solution formed, and this was filtered and acidified. A yellow precipitate resulted and this was collected, washed, dried (0·09 g.), and sublimed *in vacuo* at 250°. Bright yellow needles, m. p. 302—304°, were obtained which did not depress the m. p. of 4-hydroxy-8 : 9-benz*omeso*benzanthrone.

*4-Amino-8 : 9-benzo*mes*obenzanthrone.*—4-Hydroxy-8 : 9-benz*omeso*benzanthrone (0·6 g.) and aqueous ammonia (20 c.c. of S.G. 0·88) were heated at 220—230° for 7 hr. After being cooled, the dark red crystals were collected, washed with dilute sodium hydroxide, then water, and finally they were sublimed at 250° *in vacuo*. Bright red needles of *4-amino-8 : 9-benzo*mes*obenzanthrone* (0·32 g.), m. p. 283—286° (Found : C, 85·0; H, 4·3; N, 4·7. $C_{21}H_{13}ON$ requires C, 85·4; H, 4·4; N, 4·8%), were obtained.

We thank Imperial Chemical Industries Limited for a maintenance grant to one of us (A. J. B.) and gifts of intermediates.

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The Preparation of Nitrogen Samples for Mass-spectrographic Analyses.

By P. F. Holt and B. P. Hughes.

[Reprint Order No. 5764.]

Nitrogen obtained by the Dumas procedure for examination in the mass spectrometer may contain impurities due to incomplete combustion which cause slight errors. Incomplete combustion is avoided if a high temperature of combustion is used with a nickel oxide furnace filling. The correction for air contamination is better calculated from the argon-40 peak than from the oxygen-32 peak.

We have described (*J.*, 1953, 1666) a modified Dumas procedure which is a satisfactory alternative to Rittenberg's procedure for the preparation from isotopically labelled substances of nitrogen samples for mass-spectrographic analysis. Unlike Rittenberg's, Dumas's procedure does not necessarily produce random pairing of the atoms in the nitrogen molecules on oxidation of compounds containing two adjacent nitrogen atoms, and it is therefore useful in the study of isotope distribution in diazo-compounds. As the nitrogen is obtained from the compound in one stage, it may sometimes be preferable to Rittenberg's procedure for normal routine determinations also, particularly when dealing with multiple samples.

Errors may arise in the determination of isotope ratios owing to inclusion of impurities with a mass number identical with that of one of the isotopes measured. When nitrogen isotopes are assayed by Rittenberg's procedure, nitrous and nitric oxides may give rise to a peak at mass 30. Dr. D. H. Tomlin (personal communication) states that the correction which is made for air inadvertently introduced during the manipulation of the samples

may also be inaccurate because of oxygen derived from the hypobromite. Errors might be introduced in results derived by the Dumas procedure either by substances produced during the combustion of the sample, such as carbon monoxide and ethylene (mass 28), ethane (giving ethyl radicals, mass 29, in the mass spectrometer), and nitric oxide (mass 30), or by air present in the carbon dioxide used for sweeping out the combustion train.

Samples of nitrogen were obtained from labelled phthalimide by the method previously described but including in the combustion train a packing of iodine pentoxide kept at 130° to remove carbon monoxide. Examination of the samples in the mass spectrometer showed that a discrepancy of about 2—4% occurred in the atom % ^{15}N values according to whether they were calculated from the mass ratio 28/29 or the mass ratio 29/30 (Table 1, cols. 2 and 3, samples 1—5). This result suggested the presence of an impurity other than carbon monoxide in the nitrogen samples.

TABLE 1. *Percentage abundance of* ^{15}N *in nitrogen samples derived from labelled phthalimide.*

	Air correction base on 32 peak		Air correction base on 40 peak	
Calc. from mass ratio	28/29	29/30	28/29	29/30
Sample				
1	32·7	33·8	33·7	33·8
2	32·8	33·4	34·2	33·5
3	32·4	33·8	33·8	33·8
4	32·7	33·5	33·4	33·5
5	31·8	33·8	33·7	33·8
Mean	32·5	33·8	33·7	33·7
6	18·7	33·5	34·6	33·7
7	19·9	33·3	34·2	33·5

The presence of hydrocarbons amongst the combustion products of several organic compounds, indicating incomplete combustion of the sample, is shown both by a peak in the mass spectrum at mass 16 (Table 2, col. 2), and by a complicated spectrum above mass

TABLE 2. *Relative intensity of* 16 *peak* [(28) + (29) + (30) *taken as* 100].

Fillings	CuO	NiO	CuO + NiO
Substance			
1 Phthalimide ...	3·5, 0·73, 0·46, 2·8, 2·4	0·003, <0·001, 0·003, <0·001	0·004, 0·006
2 Azobenzene ...	0·31, 0·11, 0·97, 0·21	0·012, 0·001	0·002, 0·06, <0·001, <0·001 0·04, <0·001, 0·007, <0·001
3 Tyrosine	1·2	<0·001	—
4 Serum albumen	3·1	<0·001	—

40. The peak at mass 16 was too large to be caused by O^+ or O_2^{++} ions and was probably due to methane. Ravenswaay and Schweitzer (*Rec. Trav. chim.*, 1938, **57**, 688) reported that methane is produced in Dumas analyses, and Kirsten (*Mikrochem. Mikrochim. Acta*, 1952, **40**, 122) that copper oxide is ineffective in removing methane at temperatures below 800°. Kirsten used nickel oxide at 1050°. Nitrogen samples prepared from labelled phthalimide by Kirsten's procedure were found to be virtually free from methane and gave no complex spectrum above mass 40 (Table 2, col. 3). When nitrogen samples which contained a high abundance of ^{15}N were obtained by Kirsten's method, no peak at mass 31 could be detected, indicating that ^{15}NO was absent and that nitric oxide was not formed.

In computing the results of mass-spectrographic analysis, a correction is normally applied for traces of air which may contaminate the sample. This correction is based on the value of the 32 peak, and it is assumed that the amount of atmospheric nitrogen which has contaminated the sample bears the same ratio to the measured amount of oxygen as the abundance of nitrogen to the abundance of oxygen in the air. It is possible, however, that oxygen introduced from the atmosphere or from the carbon dioxide may be removed during the combustion, thus falsifying the correction. In Table 1, cols. 4 and 5, the results of previous analyses are recalculated, the corrections for contaminating air being based on the abundance of argon (mass 40) in the samples. It is seen that the discrepancy

between the atom % ^{15}N values as derived from the 28/29 and the 29/30 ratios disappears. Two heavily contaminated samples, numbers 6 and 7, which would normally be discarded, gave widely divergent results when corrected by the value for the 32 peak but the two results differed by only 3% when corrected by the 40 peak value. A disadvantage of using the argon peak in correcting for air contamination is that it is always very small and errors in measurement are subsequently magnified by a factor of approximately 65. Nevertheless, we have obtained more consistent results by using the argon rather than the oxygen peak for this correction.

In most experimental work which involves the use of isotopic nitrogen, only the relative abundance of the two isotopes in the samples is of interest. For this purpose it would seem that Kirsten's high-temperature combustion procedure (*loc. cit.*) using a nickel oxide filling is to be preferred.

In studying the reactions of diazo-compounds it is sometimes necessary to obtain nitrogen from labelled samples in which the pairing of at least some of the nitrogen atoms is identical with that in the original substance. For this purpose the high-temperature combustion is less satisfactory since the degree of randomization of the atoms is variable. Four consecutive combustions carried out on samples of [$^{15}N_1$]azobenzene at 1050° showed an increasing degree of random pairing in the later samples, the fractions of the N–N bonds which remained intact being 0·74, 0·71, 0·60, and 0·36. If random pairing of the nitrogen atoms takes place by a reaction catalyzed at the surface of the silica combustion tube, this effect may be due to increased roughness of the surface of the tube caused by the high temperature. When the retention of the type of pairing present in a diazo-compound is desirable, our low-temperature combustion procedure (*loc. cit.*) is preferable.

The elimination of both hydrocarbons and nitric oxide is ensured if the combustion products from the copper oxide filling at 470° are carried through a nickel oxide filling at 1050° (Table 2, col. 4).

The following values for the normal abundance of ^{15}N have been determined by examining nitrogen samples obtained by high-temperature combustion: nitrogen from azobenzene, 0·369%; from tyrosine, 0·367%; and from serum albumen, 0·369%.

Experimental

Combustion of Samples.—(1) *Low-temperature procedure.* The combustion train and nitrometer were identical with those previously described (*loc. cit.*) except that a U-tube packed with iodine pentoxide and heated in a paraffin-bath kept electrically at 130° was inserted between the combustion tube and the nitrometer.

(2) *High-temperature procedures.* A similar apparatus was used but the copper oxide filling was replaced by nickel oxide, as in Kirsten's procedure (*loc. cit.*), and this was kept electrically at 1050°. A filling of "Hopcalite," inserted between the combustion tube and the nitrometer to ensure the recombination of any dissociated carbon dioxide, was kept at 150° to prevent the condensation of water vapour. The sample was placed in the combustion tube clear of the nickel oxide and was heated in a constant stream of carbon dioxide by a movable furnace.

Other combustions were carried out using copper oxide, as in the low-temperature procedure, except that the layer of metallic copper was omitted. The main combustion tube was followed by a subsidiary tube containing nickel oxide heated to 1050°, succeeded in turn by a filling of "Hopcalite."

With respect to this and the following paper we are indebted to Dr. D. H. Tomlin who assayed our nitrogen samples, and to Imperial Chemical Industries Limited, Paints Division, for a grant (to B. P. H.).

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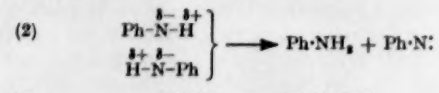
Photochemical Decomposition of Hydrazobenzene, studied by the Use of Nitrogen Isotopes.

By P. F. Holt and B. P. Hughes.

[Reprint Order No. 5765.]

The photolysis of [$^{15}N_1$]hydrazobenzene produces azobenzene which has the same isotope distribution as the starting material. Possible mechanisms of the reaction are discussed. The syntheses of [$^{15}N_1$]hydrazobenzene and [$^{15}N_1$]benzidine are described.

Weiss (*Trans. Faraday Soc.*, 1940, **36**, 856) reported that azobenzene and aniline are formed when alcoholic solutions of hydrazobenzene are irradiated with ultra-violet light of wave-length 2300—2700 Å. He proposed a mechanism for the reaction which involved homolytic fission of the hydrazobenzene molecule, followed by interaction of pairs of the resulting phenylamine radicals by mutual dipole–dipole attraction to give aniline and phenylimine radicals. The latter then dimerize, producing azobenzene:



This mechanism resembles that proposed by Stieglitz and Curme (*Ber.*, 1913, **46**, 911) to explain the thermochemical decomposition of hydrazobenzene, the mechanism of which was also studied by decomposing isotopically labelled hydrazobenzene (Holt and Hughes, *J.*, 1953, 1666). This method is applicable to the photochemical reaction; the mechanism suggested by Weiss will result in the complete randomization of the nitrogen atoms in azobenzene from hydrazobenzene labelled in one position with ^{15}N.

[$^{15}N_1$]Hydrazobenzene was prepared by reducing [$^{15}N_1$]azobenzene. An alcoholic solution of the hydrazobenzene was irradiated with light from a water-cooled mercury lamp. The azobenzene so formed was immediately separated to prevent contamination of the sample by azobenzene formed by the oxidation of hydrazobenzene in the air. Nitrogen samples were obtained by a Dumas procedure (Holt and Hughes, preceding paper), since the usual hypobromite method inevitably gives complete randomization, both from the azobenzene produced by the disproportionation and from the original azobenzene. These samples were analyzed in the mass spectrometer.

Samples of nitrogen examined in the mass spectrograph normally contain ions derived from $^{14}N^{14}N$, $^{14}N^{15}N$, $^{15}N^{15}N$. It can be shown that when random pairing occurs the ratio, $R = (^{14}N^{15}N)^2/{}^{14}N^{14}N \cdot {}^{15}N^{15}N$, has a theoretical value of 4. Higher values of R indicate that random pairing cannot have occurred for the whole sample. Some degree of randomization in the nitrogen molecules is introduced by the combustion procedure and this cannot be precisely controlled with small samples. The results of the analyses, shown in the Table, indicate that the degree of randomization introduced into the nitrogen

Substance	Atom % ^{15}N	R
Original azobenzene	16·8	8·1
Azobenzene from hydrazobenzene, expt. 1	16·9	10·6
expt. 2	16·6	9·1

obtained from the azobenzene is approximately the same as that in the nitrogen from the hydrazobenzene. This result invalidates equation (3) of the mechanism described by Weiss, but does not necessarily exclude the production of phenylamine radicals by equation (1).

Hydrazobenzene absorbs light of wave-length about 2500—2450 Å. Since the bond energy for N–H in hydrazobenzene is 88 kcal./mole (Cole and Gilbert, *J. Amer. Chem. Soc.*,

1951, **73**, 5423), the production of a hydrogen atom by dissociation of this group is energetically possible and the reaction may then follow the course :

$$\text{(4)}\quad Ph{\cdot}NH{\cdot}NHPh + h\nu \longrightarrow Ph{\cdot}NH{\cdot}NPh{\cdot} + H$$

$$\text{(5)}\quad Ph{\cdot}NH{\cdot}NPh{\cdot} \longrightarrow Ph{\cdot}N{:}NPh + H$$

$$\text{(6)}\quad Ph{\cdot}NH{\cdot}NHPh + H \longrightarrow Ph{\cdot}NH_2 + Ph{\cdot}NH{\cdot}$$

$$\text{(7)}\quad Ph{\cdot}NH{\cdot}NHPh + Ph{\cdot}NH{\cdot} \longrightarrow Ph{\cdot}NH_2 + Ph{\cdot}NH{\cdot}NPh{\cdot}$$

These chain reactions might be terminated by reactions such as

$$\text{(8)}\quad 2Ph{\cdot}NH{\cdot}NPh{\cdot} \longrightarrow Ph{\cdot}N{:}NPh + Ph{\cdot}NH{\cdot}NHPh$$

$$\text{(9)}\quad Ph{\cdot}NH{\cdot}NPh{\cdot} + Ph{\cdot}NH{\cdot} \longrightarrow Ph{\cdot}N{:}NPh + Ph{\cdot}NH_2$$

$$\text{(10)}\quad Ph{\cdot}NH{\cdot} + H \longrightarrow Ph{\cdot}NH_2$$

$$\text{(11)}\quad Ph{\cdot}NH{\cdot}NPh{\cdot} + H \longrightarrow Ph{\cdot}NH{\cdot}NHPh$$

The fact that the quantum yield of the reaction is less than unity (Weiss, *loc. cit.*) is evidence against this mechanism. A chain mechanism would not be involved, however, if reactions (5) and (6) were excluded.

A more probable mechanism is that suggested by Dewar (unpublished results reviewed by Szwarc, *Chem. Reviews*, 1950, **47**, 151) for the thermal decomposition. He suggests that the reaction is initiated by the homolytic fission of the hydrazobenzene molecule (1) and the reaction of the resulting phenylamine radicals with unchanged hydrazobenzene molecules (7). Subsequently reactions (8) and (9) may occur. This mechanism retains the first stage of homolytic fission suggested by Weiss. Weiss (*loc. cit.*) excluded a mechanism which he formulated as (12), however, as he was unable to detect hydrogen gas.

$$\text{(12)}\quad Ph{\cdot}\underset{H}{N}{\cdot} \quad {\cdot}\underset{H}{N}{\cdot}Ph \longrightarrow Ph{\cdot}N{:}N{\cdot}Ph + H$$

Experimental

[$^{15}N_1$]*Hydrazobenzene.*—Methods for the preparation of labelled hydrazobenzene from [$^{15}N_1$]azobenzene were described by Holt and Hughes (*J.*, 1953, 1666). This substance is made more conveniently by the following method. [$^{15}N_1$]Azobenzene (300 mg.), dissolved in ethanol (15 ml.), was heated under a reflux condenser, and ammonium sulphide solution (15 ml.) was added through the condenser. After 2 minutes' boiling, the flask was removed and stoppered. Cooling for 1 hr. in a refrigerator yielded a precipitate of hydrazobenzene, which was filtered off and washed, first with distilled water and then with distilled water containing dissolved sulphur dioxide. It was purified by recrystallization from aqueous ethanol (50%); m. p. 126—127° (decomp.) (yield 85—90%).

Disproportionation of [$^{15}N_1$]*Hydrazobenzene.*—[$^{15}N_1$]Hydrazobenzene (200 mg.) was transferred to a clear silica tube 11 cm. long and of 1·2 cm. diameter. Absolute ethanol (10 ml.) was added, the contents were frozen in liquid nitrogen and degassed, and the tube was sealed. The tube was placed alongside a low-pressure mercury arc lamp (Thermal Syndicate, Ltd., Type T/M5/564/0) which had a water-cooled anode and cathode, gave a maximum output at 2536 Å, and was housed inside a Dewar flask. The top of the tube was attached to a motor so that stirring could be effected by rotating the tube. A cylindrical reflector of polished aluminium was fitted close to the inner wall of the Dewar flask. To keep the apparatus cool, the flask was filled with water which was constantly changed. Irradiation of the sample was continued for 20 hr., a preliminary experiment having shown that there was no appreciable increase in the yield of azobenzene on longer irradiation.

Separation of [$^{15}N_1$]*Azobenzene.*—Hydrazobenzene is oxidized in the air. The unchanged material was therefore removed rapidly by conversion into benzidine; immediately after the tube had been opened, the contents were poured into 2N-sulphuric acid (30 ml.) containing ice (30 g.). After the ice had melted, the suspension was filtered, and the residue was washed with a little ethanol. The residue is a mixture of [$^{15}N_1$]benzidine and [$^{15}N_1$]diphenyline. The filtrate and washings containing the azobenzene were shaken with light petroleum (b. p. 40—60°), and the extract dried ($CaCl_2$). The azobenzene was purified by adsorption on alumina,

from which it was eluted with light petroleum. [$^{15}N_1$]Azobenzene (m. p. 66—67°) was obtained by evaporation of the solution; the yield from 200 mg. of hydrazobenzene was 8 mg.

The residue remaining after filtration of the azobenzene solution contains [$^{15}N_1$]benzidine sulphate, $^{15}NH_2{\cdot}C_6H_4{\cdot}C_6H_4{\cdot}^{14}NH_2{,}H_2SO_4$, from which [$^{15}N_1$]benzidine can be prepared by heating the residue with dilute alkali. [$^{15}N_1$]Benzidine, m. p. 125—126°, separates on cooling. This provides a convenient synthesis of labelled benzidine.

Preparation of Nitrogen.—Nitrogen was obtained from the samples for evaluation in the mass spectrometer by a combustion procedure (preceding paper) using a copper oxide filling followed by a nickel oxide filling.

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The Heat Capacity of Nickel Carbonyl and the Thermodynamics of its Formation from Nickel and Carbon Monoxide.

By J. E. SPICE, L. A. K. STAVELEY, and G. A. HARROW.

[Reprint Order No. 5779]

Values are given for the heat of fusion of nickel carbonyl, for its melting point, and for its heat capacity between 90° and 270° K. Some discussion follows on the thermodynamics of the reaction $Ni + 4CO \rightleftharpoons Ni(CO)_4(g)$.

FEW measurements of the thermal properties of nickel carbonyl seem to have been made, in spite of its industrial and scientific importance. Accordingly, calorimetric measurements have been made for nickel carbonyl in the liquid-oxygen range. From the results, the standard entropy of the compound has been estimated; combined with other available data, this quantity permits some discussion of the equilibrium constant and heat content change of the reaction $Ni + 4CO \rightleftharpoons Ni(CO)_4(g)$.

EXPERIMENTAL

The greater part of this work was done at Oxford, with the calorimeter and experimental method described by Staveley and Gupta (*Trans. Faraday Soc.*, 1949, **45**, 50).

The nickel carbonyl was prepared by Mayer and Wibaut's method (*Rec. Trav. chim.*, 1937, **56**, 356) and was purified by bulb-to-bulb distillation *in vacuo*, followed by vacuum-distillation at 0° with a low-temperature column. All three fractions had the same vapour pressure of 126·5 mm. at 0°, compared with Anderson's value of 133·7 mm. (*J.*, 1930, 1653) and Wallis and Beynon's value of 130 mm. (personal communication from the Mond Nickel Company). The high purity of this specimen was, however, shown by the small melting range and the absence of any marked pre-melting effect.

The calorimeter was designed for use with condensed gases and volatile liquids, and this meant that the nickel carbonyl had to be introduced by distillation from a detachable trap, the loss in weight of which gave the weight of carbonyl used. Unfortunately, some decomposition occurred during this process, as it always does when nickel carbonyl is distilled. The carbon monoxide formed was therefore removed from the vacuum-system by means of a Töpler pump and its volume measured, from which allowance was made for the nickel carbonyl lost by decomposition. The same procedure was followed when the nickel carbonyl was removed at the conclusion of the measurements, and a second figure for the weight used was thus obtained. This second figure (5·264 g.) was about 1% lower than the first (5·309 g.). Since decomposition of the nickel carbonyl during its removal from the calorimeter vessel was much more extensive than during its introduction (18% as against 3%) the first figure of 5·309 g. was considered the more reliable, and was used in the calculations. Throughout the measurements, the calorimeter vessel was filled with carbon monoxide (to a pressure of about half an atmosphere at room temperature) in order to prevent decomposition of nickel carbonyl vapour at the higher temperatures.

Measurements of the heat of fusion of nickel carbonyl were made subsequently at Liverpool, in order to provide some check on the reliability of the Oxford results. (It should be emphasised that any systematic error in these results is due to the uncertainty in the weight of nickel carbonyl in the calorimeter, and not to any other defect in the experimental method.) A

different type of calorimeter was used (details will appear in a forthcoming paper) in which the weight of carbonyl in the calorimeter vessel was found without ambiguity by direct weighing. The calorimeter vessel was much larger than in the Oxford apparatus, holding about 50 c.c. of liquid as against about 5 c.c. In this later work, the nickel carbonyl was kindly supplied by the Mond Nickel Company; the only impurity was stated to be about 0·003% of iron pentacarbonyl, and the compound was therefore used without further purification.

Results

Melting Point and Purity.—The following figures were obtained for the melting point of the nickel carbonyl, by using the Oxford calorimeter :

Percentage melted	30	48	65	83
Temperature (°K)	$253{\cdot}84_8$	$253{\cdot}84_9$	$253{\cdot}85_1$	$253{\cdot}85_2$

The usual extrapolation gives 253·86° K as the m. p. of the pure compound, and from the melting range, the liquid-soluble solid-insoluble impurity in the carbonyl is found to amount to 0·01 mole %.

The only value in the literature for the m. p. of nickel carbonyl is that of −25° (248° K) given by Mond (*J.*, **1890**, **57**, 749). The present value, nearly 6° higher, is probably correct to ±0·05° K, the uncertainty being due to the temperature scale used in this work. Wallis (personal communication from the Mond Nickel Company) gives the m. p. as 254·0° K.

Heat Capacity.—Heat-capacity measurements extended from 90° K to the ice-point, and values taken from the smoothed curve are given in the Table at temperature intervals of 5°. The mean percentage deviation of the experimental heat-capacity values from the smoothed curve amounts to 0·65% over the whole range, and to 0·5% over the range from

Temp. (K)	C_p (cal./mole)	Temp. (K)	C_p (cal./mole)	Temp. (K)	C_p (cal./mole)	Temp. (K)	C_p (cal./mole)
90°	21·80	145°	29·95	200°	35·61	Fusion	
95	22·64	150	30·64	205	35·92	255°	48·03
100	23·43	155	31·30	210	36·21	260	48·09
105	24·19	160	31·91	215	36·49	265	48·15
110	24·92	165	32·51	220	36·74	270	48·23
115	25·61	170	33·00	225	37·00	275	48·32 †
120	26·32	175	33·50	230	37·25	280	48·42
125	27·03	180	33·95	235	37·46	285	48·54
130	27·77	185	34·39	240	37·66	290	48·67
135	28·50	190	34·80	245	37·82 *	295	48·80
140	29·25	195	35·21	250	37·93 *	300	48·94

* Corr. for pre-melting. † From this point onwards, values were determined by extrapolation of the smoothed curve, and are therefore subject to a greater uncertainty than the other values.

125° K upwards. The possible error in the heat capacity of the empty calorimeter (which of course is used in deriving the molar heat capacity of the carbonyl) is taken into account in obtaining these values, so that the possible unsystematic error of the experimental heat capacities is as just stated.

Heat of Fusion.—The following values were obtained with the Oxford calorimeter : 3305·6, 3308·1, 3303·3 cal./mole (mean, 3306 ± 2·5). The confirmatory measurements at Liverpool were made when the calorimetric technique used was relatively undeveloped; consequently, the results showed less agreement among themselves. Four values for the heat of fusion were obtained, with a mean value of 3295 ± 15 cal./mole. Having regard to this greater uncertainty, it is felt that these " Liverpool " results do confirm the " Oxford " values for the heat of fusion and hence for the heat capacity of nickel carbonyl. It should in any case be noted that the figure taken for the weight of nickel carbonyl in the Oxford calorimeter is an upper limit for this quantity. Had the calorimeter actually contained less carbonyl, a higher rather than a lower value would be indicated for the heat of fusion. Thus, we feel that the heat capacities quoted can be relied upon to ~±0·8%, and the heat of fusion to ~±0·25%.

Standard Entropy.—Although heat capacities have not been measured for temperatures

below 90° K, it is of interest to estimate the standard entropy of nickel carbonyl. The method of extrapolation developed by Parks and his co-workers (Kelley, Parks, and Huffman, *J. Phys. Chem.*, 1929, **33**, 1802; Parks, Shomate, Kennedy, and Crawford, *J. Chem. Phys.*, 1937, **5**, 359) may be used. In this, the heat capacities at 90° and 120° K, derived from the experimental heat-capacity curve, are compared with the corresponding values taken from a " standard " curve extending down to liquid-hydrogen temperatures. The experimental curve is thus extrapolated to liquid-hydrogen temperatures, and a value for the entropy at 90° is derived. Parks *et al.* concluded that a considerable number of compounds could be grouped into two classes, each with its standard curve. The method has no adequate theoretical foundation, but in practice gives fairly reliable results provided that the molecules are not too different in size and shape from those of the " standard " substances. In the present case, the comparison has been made not only with Parks's " Class I " and " Class II " compounds but also, according to the same method, with 2 : 3 : 4-trimethylpentane, for which the heat capacities were measured by Pitzer and Scott (*J. Amer. Chem. Soc.*, 1941, **63**, 2419). The resulting values for the entropy at 90° K of solid nickel carbonyl are 18·31, 20·63, and 20·58 cal. $°K^{-1}$ $mole^{-1}$ respectively, when these three comparisons are made. As expected, there is some uncertainty, and in the absence of more precise information we take the entropy at 90° K of nickel carbonyl as 20·6 cal. $°K^{-1}$ $mole^{-1}$. Needless to say, the use of an extrapolation procedure will introduce a large error into the final figure for the entropy, if the compound actually undergoes a solid transition within the extrapolation region. Nickel carbonyl is unlikely to do this since its entropy of fusion (13·0 cal. $°K^{-1}$ $mole^{-1}$) is comparable with the entropies of fusion of solids of similar molecular shape and complexity, which also lack transitions.

Many different values have been reported for the heat of vaporisation of nickel carbonyl. Those derived from vapour-pressure data include 6500 (Dewar and Jones, *Proc. Roy. Soc.*, 1903, *A*, **71**, 427), 6700 (Wallis and Beynon, *loc. cit.*), 6920 (Anderson, *loc. cit.*), and 7200 cal./mole (Suginuma and Satozaki, *Bull. Inst. Phys. Chem. Res., Tokyo*, 1942, **21**, 432). The mean of two direct determinations by Wallis and Beynon (*loc. cit.*) gave 6300 cal./mole. We shall now assume a value of 6500 cal./mole at 298·16° K, since we attach greater weight to the value determined directly than to the values obtained from vapour-pressure measurements. Although this value is probably the best obtainable from the existing data, the entropy of vaporisation thus calculated (21·8 cal. $°K^{-1}$ $mole^{-1}$ at 298·16° K) is lower than would be expected from the Hildebrand–Trouton rule (Hildebrand, *J. Chem. Phys.*, 1939, **7**, 233). Thus, the entropy of vaporisation of carbon tetrachloride at the same molecular concentration of the saturated vapour is 22·2; yet nickel carbonyl is a less compact molecule than carbon tetrachloride, and so might be expected to have a greater entropy of vaporisation.

The standard entropy of nickel carbonyl is now computed as follows:

	cal. $°K^{-1}$ $mole^{-1}$
S for solid at 90° K (Parks's extrapolation)	20·6
ΔS for solid, 90—253·86° K, graphical	31·5
$\Delta S_{fusion} = 3306/253{\cdot}86$	13·0
ΔS for liquid, 253·86—298·16° K, graphical	9·8
$\Delta S_{vaporisation} = 6500/298{\cdot}16$	21·8
Entropy for vapour at 298·16° K and 38·7 cm.*	96·7
ΔS for compression from 38·7 to 76 cm.	−1·3
$S°$ for $Ni(CO)_4$ (298·16° K)	95·4

* Wallis and Beynon, *loc. cit.*

(Because of the manifest uncertainties in the above calculation, it is not worth while to apply the correction for gas imperfections.)

Crawford and Cross (*J. Chem. Phys.*, 1938, **6**, 525) calculated the thermodynamic functions of nickel carbonyl from their assignment of the vibration frequencies of this molecule, and they obtain $S°$ (at 298·16° K) = 97·0. In view of the approximate nature of the present calculation, the agreement between calorimetric and spectroscopic entropies is as close as could be expected.

THE THERMODYNAMICS OF THE FORMATION OF NICKEL CARBONYL FROM NICKEL AND CARBON MONOXIDE.

Equilibrium Measurements.—Mittasch (*Z. physikal. Chem.*, 1902, **40**, 1) carried out an exhaustive study of the equilibrium $Ni + 4CO(g) \rightleftharpoons Ni(CO)_4(g)$ and we shall now consider his results together with information on the heat content and entropy changes for this reaction. Mittasch used a static method, and his equilibrium constants, although self-consistent and reproducible for a given filling of his apparatus, varied markedly from one filling to another, and in particular were greatly influenced by the physical form of the metallic nickel present in the vessel.

Mittasch (*loc. cit.*, pp. 21 and 23) gives an expression for $K = [CO]^4/[Ni(CO)_4]$, the equilibrium constant of the decomposition reaction, which is actually neither K_c nor K_p. Moreover, the values of K given later in the paper are in fact calculated from the expression $(p - P)^4/[27(4P - p)(1 + \alpha\theta)^3]$, and not from the corresponding expression involving $(p - P)$ rather than $(p - P)^4$ which appears in error on pp. 21 and 23 of the paper. In Mittasch's notation, P (sometimes P_θ) is the pressure in mm. which would have been exerted by the nickel carbonyl vapour at $\theta°$ C, if no decomposition had occurred; p (or p_θ) is the actual pressure in mm. at $\theta°$ C; α is the temperature coefficient of the pressure of a perfect gas. The correct expression for the equilibrium constant of the formation reaction is:

$$K_p = p_{Ni(CO)_4}/p_{CO}^4 = \frac{(4P - p) \times 27 \times 760^3}{(p - P)^4 \times 256}$$

The relation between this K_p and Mittasch's K is:

$$\log_{10} K_p = -\log_{10} K + 6{\cdot}234 - 3 \log_{10} (1 + \alpha\theta)$$

Mittasch gives three main series of equilibrium results—series 2, 5, and 6 on pp. 46—47 of his paper—and for each series $\log_{10} K_p$, when recalculated as above, gives a good linear plot against $1/T$. The interpolated values of $\log_{10} K_p$ at 298° K, together with the corresponding $\Delta H°$ and $\Delta G°$ values for the reaction, are then as follows:

	$\log_{10} K_p$ at 298° K	$\Delta G°$ (kcal.)	$\Delta H°$ (kcal.)
Series 2	1·67	−2·3	−26
Series 5	2·62	−3·6	−27·5
Series 6	3·32	−4·5	−30

Heat of Reaction.—Reicher ("Werken von het Genootschap ter bevordering der natuur-, genees- en heelkunde," Amsterdam, 1896, 2nd Series, Vol. II, p. 296) found the heat of combustion of liquid nickel carbonyl at constant volume to be 270·8 kcal./mole. Combining this with the aforementioned figure of 6·5 kcal./mole for the heat of vaporisation, and with accepted values for the other necessary heats of formation ("Selected Values of Chemical Thermodynamic Properties," Nat. Bur. Standards, Circular 500), we obtain for the reaction $Ni + 4CO\ (g) \rightleftharpoons Ni(CO)_4\ (g)$, $\Delta H° = -52{\cdot}6$ kcal. Mittasch (*loc. cit.*, p. 48), using a direct method, found the heat of formation of liquid nickel carbonyl from nickel and carbon monoxide at constant pressure to be 52·17 kcal./mole. From this, the value for gaseous nickel carbonyl is $\Delta H° = -45{\cdot}67$ kcal. Finally, experiments carried out in the Clydach laboratory of the Mond Nickel Company (personal communication from the Company) gave values of −34·5 kcal. (direct method) and −36·3 kcal. (indirect method). The values are summarised as follows:

$\Delta H°$ (*kcal.*) *for the reaction* $Ni + 4CO\ (g) \rightleftharpoons Ni(CO)_4\ (g)$.

From heat of combustion (Reicher)		−52·6
Direct determination (Mittasch)		−45·7
From d $(\log_{10} K_p)/dT$ (Mittasch):	Series 2	−26·0
	Series 5	−27·5
	Series 6	−30·0
Direct determination (Mond Nickel Co., 1936)		−34·5
Indirect determination (Mond Nickel Co., 1950)		−36·3

The discrepancies are somewhat startling. Reicher gives little information about his experimental method, but Mittasch's direct determinations were apparently well-planned and carefully executed. One would not expect the values from the temperature coefficient

of the equilibrium constant to be as reliable as the results of direct determinations (especially in view of the uncertainty attaching to Mittasch's equilibrium constants), so we accept the two modern determinations made by the Mond Nickel Company as likely to be the most accurate. Accordingly, we take a mean value of $\Delta H^\circ = -35$ kcal. This gives, for the formation of nickel carbonyl from its elements, $\Delta H_f^\circ = -140{\cdot}6$ kcal./mole for the gaseous compound, and $\Delta H_f^\circ = -147{\cdot}1$ kcal./mole for the liquid.

ΔS° and ΔG° for the Reaction.—We use the following values for standard entropies (at 298·16° K):

Nickel carbonyl	97·0	(Crawford and Cross, *loc. cit.*)
Nickel	7·14	(Busey and Giauque, *J. Amer. Chem. Soc.*, 1952, **74**, 3157)
Carbon monoxide	47·30	(Clayton and Giauque, *ibid.*, 1932, **54**, 2610)

Then for the formation of gaseous nickel carbonyl from nickel and carbon monoxide, we have $\Delta S^\circ = -99{\cdot}3$ cal. $^\circ K^{-1}$ mole^{-1} (at 298·16° K). Combining this with the above value for ΔH°, we have $\Delta G^\circ = -5{\cdot}4$ kcal., and $\log_{10} K_p = 3{\cdot}96$ (at 298·16° K) for the reaction $Ni + 4CO \rightleftharpoons Ni(CO)_4(g)$. These values seem in fairly satisfactory agreement with those derived from Mittasch's equilibrium measurements ($\Delta G^\circ = -2{\cdot}3$ to $-4{\cdot}5$ kcal.; $\log_{10} K_p = 1{\cdot}67$—$3{\cdot}32$) in view of the uncertainties inherent in the whole question.

The scatter of Mittasch's results is undoubtedly due to variations in the chemical potential of the solid nickel in equilibrium with gaseous nickel carbonyl and carbon monoxide. Giauque (*J. Amer. Chem. Soc.*, 1949, **71**, 3192) has recently shown that the true equilibrium corresponding to a solid, macrocrystalline phase in contact with gases, may be impossible of attachment when the solid is present in a finely divided form. Thus, the heat content of finely divided magnesium oxide, made by dehydrating the hydroxide *in vacuo* at a fairly low temperature, was greater by 888 cal./mole than that of crystalline magnesium oxide, while the free energy was greater by 800 cal./mole. Giauque attributes this difference to the possession by the finely divided sample of a more open structure, of higher energy content, than that of the macrocrystalline phase. The same thing may well be true of the metallic nickel present in the nickel carbonyl equilibrium, although the numerical data are not sufficiently precise to permit even a semiquantitative discussion in these terms. The experimental realisation of the equilibrium under discussion must necessarily involve finely divided nickel, so that it may be that significant equilibrium constants cannot possibly be obtained by direct measurements. Moreover, a direct determination of ΔH° must similarly involve finely divided nickel, and a significant value for this quantity may have to be derived from accurate determinations of the heat of combustion of nickel carbonyl.

Since the completion of the main part of this paper, we have seen a preliminary report of direct measurements of the nickel–nickel carbonyl equilibrium over the temperature range 49—94° C (Tomlinson, Abst. Papers presented at the 125th Mtg. Amer. Chem. Soc., March 1954, p. 180). The results are summarised in the equation ΔG° (cal.) $= -31{,}972 + 87{\cdot}92T$ (°K), for the reaction $Ni + 4CO \rightleftharpoons Ni(CO)_4(g)$, whence ΔG° (at 298·16° K) $= -5{\cdot}8$ kcal., in good agreement with our value of $-5{\cdot}4$ kcal., derived from the heat content and entropy changes for the reaction. The above equation, however, also gives $\Delta H^\circ = -32{\cdot}0$ kcal. and ΔS° (at 298·16° K) $= -87{\cdot}9$ cal. $^\circ K^{-1}$ mole^{-1}, and Tomlinson claims that the latter figure indicates that Crawford and Cross's value of 97·0 for the standard entropy of nickel carbonyl is about 11 cal. $^\circ K^{-1}$ mole^{-1} (or 10%) too low. We would merely point out (*a*) that our calorimetric measurements confirm Crawford and Cross's value, and could not possibly give a value as high as 108 cal. $^\circ K^{-1}$ mole^{-1} for the standard entropy of nickel carbonyl, and (*b*) that Tomlinson's values for ΔH° and ΔS° are based on the temperature coefficient of ΔG°, and are therefore subject to greater uncertainty than ΔG° itself.

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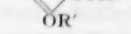
The Benzoylation and Benzylation of C-Methylphloracetophenones.

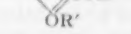
By W. B. Whalley.

[Reprint Order No. 5798.]

Benzoylation and benzylation studies of *C*-methylphloracetophenones have furnished routes to several new derivatives of *C*-methylphloracetophenone and to novel syntheses of 5 : 7 : 4′- and 5 : 7 : 2′-trimethoxy-6-methyl*iso*flavone.

Whilst the benzoylation of phloracetophenone gives exclusively 4-benzoyloxy-2 : 6-dihydroxyacetophenone (Canter, Curd, and Robertson, *J.*, 1933, 1245), *C*-methylphloracetophenone always gives a mixture of 4 : 6-dibenzoyloxy-2-hydroxy-3-methylacetophenone (I; R = R′ = Ph·CO, R″ = Me) and 6-benzoyloxy-2 : 4-dihydroxy-3-methylacetophenone (I; R′ = Ph·CO, R = H, R″ = Me) together with small amounts of unchanged *C*-methylphloracetophenone. The orientation of the monobenzoyl compound was readily established by methylation to 6-benzoyloxy-2 : 4-dimethoxy-3-methylacetophenone (II; R = R″ = Me, R′ = Ph·CO) followed by debenzoylation to the well-authenticated 6-hydroxy-2 : 4-dimethoxy-3-methylacetophenone (II; R′ = H, R = R″ = Me). Methylation of the dibenzoyl compound gave the ether (II; R = R′ = Ph·CO, R″ = Me) which was de-esterified to yield the hitherto unknown 4 : 6-dihydroxy-2-methoxy-3-methylacetophenone (II; R = R′ = H, R″ = Me), albeit in rather low overall yield.

(I) 

(II) 

The orientation of the phenol (II; R = R′ = H, R″ = Me) and hence of the cognate derivatives was established by the non-identity of the ketone with the remaining two isomeric *O*-monomethyl-*C*-methylphloracetophenones and by ethylation to 4 : 6-diethoxy-2-methoxy-3-methylacetophenone (II; R = R′ = Et, R″ = Me) which was also obtained by the methylation of 4 : 6-diethoxy-2-hydroxy-3-methylacetophenone.

Methylation of 4 : 6-dimethoxy-2-hydroxy-3-methylacetophenone (I; R = R′ = R″ = Me) which cannot be accomplished by the use of methyl iodide in acetone containing potassium carbonate (cf. Curd and Robertson, *J.*, 1933, 437) proceeds smoothly with methyl sulphate.

Benzylation of *C*-methylphloracetophenone (I; R = R′ = H, R″ = Me) furnished the 4 : 6-dibenzyl ether (I; R = R′ = Ph·CH_2, R″ = Me) which was converted into the methyl ether (II; R = R′ = Ph·CH_2, R″ = Me) and thence by catalytic debenzylation successively into (II; R = Ph·CH_2, R′ = H, R″ = Me) and (II; R = R′ = H, R″ = Me). Similarly 2 : 4 : 6-trihydroxy-4′-methoxy-3-methyldeoxybenzoin (I; R = R′ = H, R″ = *p*-MeO·C_6H_4·CH_2) (Whalley, *J. Amer. Chem. Soc.*, 1953, **75**, 1059) gave the 4 : 6-dibenzyl ether and thence the 4 : 6-dibenzyl 2 : 4′-dimethyl ether (II; R = R′ = Ph·CH_2, R″ = *p*-MeO·C_6H_4·CH_2), 6-hydroxy-2 : 4 : 4′-trimethoxy-3-methyldeoxybenzoin (II; R = Me, R′ = H, R″ = *p*-MeO·C_6H_4·CH_2), and 5 : 7 : 4′-trimethoxy-6-methyl*iso*flavone (Whalley, *loc. cit.*), thereby providing further evidence for the structure of this compound. Similarly, 5 : 7 : 2′-trimethoxy-6-methyl*iso*flavone (Whalley, *J.*, 1953, 3366) was synthesised from 2 : 4 : 6-trihydroxy-2′-methoxy-3-methyldeoxybenzoin.

Experimental

Benzoates of C-Methylphloroglucinol.—Benzoyl chloride (4·5 g.) was added with stirring in six portions during 10 min. to *C*-methylphloroglucinol (5 g.) in 2% sodium hydroxide solution (100 ml.) at 0°. The mixture was acidified to Congo-red and the sticky precipitate purified from methanol to give 4 : 6-*dibenzoyloxy-2-hydroxy-3-methylacetophenone* in prisms (1—1·3 g.), m. p. 149°, having an intense red-brown ferric reaction in alcohol (Found: C, 70·5; H, 4·8. $C_{23}H_{18}O_6$

requires C, 70·8; H, 4·7%). Concentration of the methanolic mother-liquors furnished **6-*benzoyloxy*-2 : 4-*dihydroxy*-3-*methylacetophenone*** in colourless prisms (1 g.), m. p. 189° (from methanol), having an intense red-brown ferric reaction in alcohol (Found : C, 67·3; H, 4·7. $C_{16}H_{14}O_5$ requires C, 67·1; H, 4·9%). Methylation of this ketone (2 g.) by methyl sulphate–acetone–potassium carbonate gave **6-*benzoyloxy*-2 : 4-*dimethoxy*-3-*methylacetophenone***, which separated from aqueous methanol in tablets (2 g.), m. p. 89°, having a negative ferric reaction in alcohol [Found : C, 68·3; H, 5·6; OMe, 19·6. $C_{16}H_{12}O_3(OMe)_2$ requires C, 68·8; H, 5·8; OMe, 19·7%].

Hydrolysis of this ester (1 g.) with aqueous-methanolic 3N-potassium hydroxide (15 ml.) during 2 hr. at room temperature followed by isolation with ether furnished 6-hydroxy-2 : 4-dimethoxy-3-methylacetophenone (0·5 g.), m. p. 35°, having an intense violet ferric reaction in alcohol. Lindstedt and Misiorny (*Acta Chim. Scand.*, 1952, **6**, 1212) record m. p. 38—39°.

4 : 6-*Dihydroxy*-2-*methoxy*-3-*methylacetophenone* (II; R = R′ = H, R″ = Me).—(*a*) Methylation of **4 : 6-dibenzoyloxy-2-hydroxy-3-methylacetophenone** (3 g.) during 24 hr., in boiling acetone containing potassium carbonate and methyl sulphate, furnished 4 : 6-dibenzoyloxy-2-methoxy-3-methylacetophenone as a colourless oil (3 g.), devoid of a ferric reaction and hydrolysed during 2 hr. at room temperature by aqueous-methanolic 3N-potassium hydroxide (30 ml.). **4 : 6-*Dihydroxy*-2-*methoxy*-3-*methylacetophenone*** (0·7 g.), isolated by ether, was purified from benzene in very pale yellow plates, m. p. 142°, unchanged by sublimation at 180°/0·01 mm. and having an intense red-brown ferric reaction in alcohol (Found : C, 62·0; H, 6·4; OMe, 15·5. $C_9H_9O_3$·OMe requires C, 61·3; H, 6·2; OMe, 15·8%). (*b*) Benzylation of *C*-methylphloracetophenone (4 g.) with benzyl bromide (7·6 g., 2 mols.) in boiling acetone (75 ml.) containing potassium carbonate (15 g.) during 8 hr. gave **4 : 6-*dibenzyloxy*-2-*hydroxy*-3-*methylacetophenone***, prisms (from methanol) (2·5 g.), m. p. 145°, having an intense red-brown ferric reaction in alcohol (Found : C, 75·7; H, 5·8. $C_{23}H_{22}O_4$ requires C, 76·2; H, 6·1%). The yield could not be increased by variation in the conditions.

Methylation of this benzyl ether (3 g.) by methyl sulphate–acetone–potassium carbonate during 24 hr. furnished **4 : 6-*dibenzyloxy*-2-*methoxy*-3-*methylacetophenone*** which separated from methanol in prisms (3 g.), m. p. 79°, having a negative ferric reaction in alcohol (Found : C, 76·1; H, 6·0. $C_{24}H_{24}O_4$ requires C, 76·6; H, 6·4%). Debenzylation of this ether (2 g.) in acetic acid (50 ml.) with palladium–charcoal occurred during 10 min. to furnish 4 : 6-dihydroxy-2-methoxy-3-methylacetophenone (1·1 g.) identical with the product prepared by method (*a*).

This ketone in boiling acetone containing methyl sulphate and potassium carbonate yielded quantitatively in 2 hr. **2 : 4 : 6-*trimethoxy*-3-*methylacetophenone*** which was most readily purified by distillation to yield a colourless oil which rapidly solidified in plates, m. p. 44°, insoluble in 2N-sodium hydroxide, devoid of a ferric reaction in alcohol, very soluble in all the usual organic solvents, and identical with a specimen prepared in 90% yield by the methylation of 2-hydroxy-4 : 6-dimethoxy-3-methylacetophenone by methyl sulphate–potassium carbonate–acetone (48 hr.) [Found : C, 64·7; H, 7·4; OMe, 40·6. $C_9H_7O(OMe)_3$ requires C, 64·3; H, 7·2; OMe, 41·5%].

4 : 6-*Diethoxy*-2-*methoxy*-3-*methylacetophenone* (II; R = R′ = Et, R″ = Me).—*C*-Methylphloracetophenone (4 g.) with ethyl iodide or ethyl sulphate in boiling acetone containing potassium carbonate furnished **4 : 6-*diethoxy*-2-*hydroxy*-3-*methylacetophenone*** (I; R = R′ = Et, R″ = Me) in pale yellow needles (4 g.), m. p. 147°, from alcohol [Found : C, 65·2; H, 7·7; OEt, 37·7. $C_9H_8O_2(OEt)_2$ requires C, 65·5; H, 7·6; OEt, 37·8%], with an intense red-brown ferric reaction in alcohol and sparingly soluble in this solvent. Methylation of this ketone proceeded quantitatively during 50 hr. on use of methyl sulphate and potassium carbonate in boiling acetone, to yield **4 : 6-*diethoxy*-2-*methoxy*-3-*methylacetophenone*** in prisms, m. p. 51°, from aqueous methanol (Found : C, 66·3; H, 8·0. $C_{14}H_{20}O_4$ requires C, 66·6; H, 8·0%), identical with the ethylation product of 4 : 6-dihydroxy-2-methoxy-3-methylacetophenone.

4-*Hydroxy*-2 : 6-*dimethoxy*-3-*methylacetophenone* (II; R = H, R′ = R″ = Me).—(*a*) 4 : 6-Dihydroxy-2-methoxy-3-methylacetophenone (1 g.) with benzyl bromide (1 g.) in boiling acetone (25 ml.) containing potassium carbonate (4 g.) during 3½ hr. gave **4-*benzyloxy*-6-*hydroxy*-2-*methoxy*-3-*methylacetophenone***, needles (from methanol) (0·7 g.), m. p. 105°, having an intense green-brown ferric reaction in alcohol (Found : C, 71·2; H, 6·6; OMe, 11·1. $C_{16}H_{16}O_5$·OMe requires C, 71·3; H, 6·3; OMe, 10·8%). Methyl sulphate–acetone–potassium carbonate converted it quantitatively into 4-benzyloxy-2 : 6-dimethoxy-3-methylacetophenone, an oil, which on hydrogenolysis in acetic acid with palladium–charcoal gave quantitatively **4-*hydroxy*-2 : 6-*dimethoxy*-3-*methylacetophenone***, needles (from methanol), m. p. 121°, devoid of a ferric reaction in alcohol and oxidised readily in solution [Found : C, 62·6; H, 6·8; OMe, 28·3.

$C_9H_8O_2(OMe)_2$ requires C, 62·8; H, 6·7; OMe, 29·5%]. (*b*) **4 : 6-Dibenzyloxy-2-methoxy-3-methylacetophenone** (2 g.) in methanol (30 ml.) containing a catalyst [prepared from charcoal (0·5 g.) and palladium chloride (30 ml. of 1% solution)] rapidly (5 min.) absorbed hydrogen (126 ml., 1 mol.). Isolation of the product at this stage furnished 4-benzyloxy-6-hydroxy-2-methoxy-3-methylacetophenone (1·3 g.), identical with that prepared by method (*a*).

5 : 7 : 4′-*Trimethoxy-6-methylisoflavone*.—Prepared by the addition during 3 hr. of benzyl bromide (6 g., 2 mols.) to **2 : 4 : 6-trihydroxy-4′-methoxy-3-methyldeoxybenzoin** (Whalley, *J. Amer. Chem. Soc.*, 1953, **75**, 1059) (5 g.) in boiling acetone (100 ml.) containing potassium carbonate (20 g.) and isolated in the usual manner after a further 3 hr., **4 : 6-*dibenzoyloxy*-2-*hydroxy*-4′-*methoxy*-3-*methyldeoxybenzoin*** separated from methanol (sparingly soluble) in prisms (3 g.), m. p. 129°, exhibiting an intense red-brown ferric reaction in alcohol (Found : C, 76·9; H, 6·4; OMe, 7·0. $C_{29}H_{26}O_4$·OMe requires C, 76·9; H, 6·0; OMe, 6·6%). This ketone (5 g.) with methyl sulphate–acetone–potassium carbonate furnished during 40 hr. **4 : 6-*dibenzyloxy*-2 : 4′-*dimethoxy*-3-*methyldeoxybenzoin*** in prisms (5 g.) (from methanol), m. p. 106°, having a negative ferric reaction in alcohol [Found : C, 76·8; H, 6·8; OMe, 13·2. $C_{29}H_{24}O_3(OMe)_2$ requires C, 77·2; H, 6·3; OMe, 12·9%].

The ketone (3·6 g.) in acetic acid (150 ml.) containing a catalyst prepared from charcoal (1 g.) and palladium chloride (30 ml.; 1% solution) absorbed hydrogen (375 ml., 2 mols.) during 10 min. After removal of the solvent under reduced pressure **4 : 6-*dihydroxy*-2 : 4′-*dimethoxy*-3-*methyldeoxybenzoin*** separated from methanol in needles (2·7 g.), m. p. 176°, having an intense olive-green ferric reaction in alcohol [Found : C, 67·4; H, 6·0; OMe, 20·5. $C_{18}H_{18}O_5(OMe)_2$ requires C, 67·5; H, 6·0; OMe, 20·5%]. Methylation of the ketone (1 g.) during 1½ hr. in boiling acetone (50 ml.) containing potassium carbonate (3 g.) and excess of methyl iodide gave **6-*hydroxy*-2 : 4 : 4′-*trimethoxy*-3-*methyldeoxybenzoin*** in needles (1 g.), m. p. 88°, from aqueous methanol [Found : C, 68·4; H, 6·3; OMe, 29·5. $C_{18}H_{11}O_3(OMe)_3$ requires C, 68·3; H, 6·4; OMe, 29·4%]. The compound has an intense green ferric reaction in alcohol. Cyclisation of this ketone (1·5 g.) by sodium–ethyl formate gave **5 : 7 : 4′-trimethoxy-6-methyl*iso*flavone** (0·8 g.), identical with the product prepared by the *C*-methylation of genistein (Whalley, *loc. cit.*).

5 : 7 : 2′-*Trimethoxy-6-methylisoflavone*.—Prepared as described previously, from **2 : 4 : 6-trihydroxy-2′-methoxy-3-methyldeoxybenzoin** (Whalley, *loc. cit.*) (4 g.), **4 : 6-*dibenzyloxy*-2-*hydroxy*-2′-*methoxy*-3-*methyldeoxybenzoin*** separated from methanol (sparingly soluble) in needles (2 g.), m. p. 146°, having an intense violet-red ferric reaction in alcohol (Found : C, 76·9; H, 6·0; OMe, 7·2. $C_{29}H_{26}O_4$·OMe requires C, 76·9; H, 6·0; OMe, 6·6%). This ketone (5 g.) furnished **4 : 6-*dibenzyloxy*-2 : 2′-*dimethoxy*-3-*methyldeoxybenzoin*** which separated from methanol in prisms (5 g.), m. p. 107°, devoid of a ferric reaction in alcohol [Found : C, 76·8; H, 6·7; OMe, 13·5. $C_{29}H_{24}O_3(OMe)_2$ requires C, 77·2; H, 6·3; OMe, 12·9%].

Catalytic debenzylation in acetic acid, quantitative in 20 min., gave **4 : 6-*dihydroxy*-2 : 2′-*dimethoxy*-3-*methyldeoxybenzoin*** which separated from light petroleum (b. p. 60—80°) in plates, m. p. 118°, exhibiting an intense green ferric reaction in alcohol [Found : C, 67·6; H, 6·0; OMe, 20·7. $C_{18}H_{18}O_5(OMe)_2$ requires C, 67·5; H, 6·0; OMe, 20·5%]. Methylation of this deoxybenzoin (0·8 g.) by methyl iodide–acetone–potassium carbonate during 30 min. gave 6-hydroxy-2 : 4 : 2′-trimethoxy-3-methyldeoxybenzoin (0·8 g.) identical with the previous specimen (Whalley, *loc. cit.*) and converted by sodium–ethyl formate into **2-*hydroxy*-5 : 7 : 2′-*trimethoxy*-6-*methyl*isoflavanone** which separated from methanol in tablets (0·5 g.), m. p. 196—197° (decomp.), devoid of a ferric reaction in alcohol (Found : C, 65·8; H, 5·7. $C_{19}H_{20}O_6$ requires C, 66·3; H, 5·9%). This *iso*flavanone was converted quantitatively in boiling acetic acid (10 min.) into **5 : 7 : 2′-trimethoxy-6-methyl*iso*flavone** (Whalley, *loc. cit.*).

The author thanks Mr. G. Lloyd, B.Sc., for the preparation of *o*- and *p*-methoxybenzyl cyanide, and Smith, Kline, and French Laboratories, Philadelphia, for a generous gift of *C*-methylphloroglucinol.

THE UNIVERSITY OF LIVERPOOL [*Received, September 12th*, 1954.]

Association Complexes of Aromatic Organometallic Halides in Solution.

By W. Slough and A. R. Ubbelohde.

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Experiments are reported on the lowering of vapour pressure of solutions in diethyl ether of magnesium bromide or a Grignard compound, RMgX (R = *cyclo*hexyl, phenyl, *p*-tolyl, *o*-tolyl, or *p*-methoxyphenyl). Estimates have thus been obtained of the effect of the nature of R on the degree of association at different concentrations and temperatures. The bromine atom acts as a powerful centre promoting association of the Grignard compounds. Some associating power is also found in the organic groups, but any differences between the groups studied are small. Effects of traces of oxygen in promoting polymerisation are described.

The formation of association complexes in solutions of Grignard reagents can influence the course of Grignard reactions (Mackle and Ubbelohde, *J.*, 1948, 1161) in ways which may be important in syntheses and in the control of stoicheiometry required for calorimetric studies (Nichol and Ubbelohde, *J.*, 1952, 415). Complex formation may also be relevant for the interpretation of electron-deficient bonds involving organic groups, as in hexamethyldialuminium (Rundle, *J. Amer. Chem. Soc.*, 1947, **69**, 1327; *J. Chem. Phys.*, 1949, **17**, 671; Lewis and Rundle, *ibid.*, 1953, **21**, 986), and of polarisation bonds as in *p*-nitroaniline [McKeown, Ubbelohde, and (Miss) Woodward, *Acta Cryst.*, 1951, **4**, 391].

Published information on the molecular weights and association of Grignard compounds in solution is conflicting. Observations described on p. 111 suggest that part of the confusion may arise through the effects of oxygen in promoting polymerisation. Such effects may not have been completely excluded in all the results reported hitherto. From ebulliometric determination of the molecular weights Meisenheimer and Schlichenmaier (*Ber.*, 1928, **61**, 720) claimed that methylmagnesium iodide, ethylmagnesium bromide, and phenylmagnesium bromide exist in the monomeric form for concentrations less than 0·1M in diethyl ether. With increasing concentration the molecular weight increases, and it tends towards $(RMgX)_2$ for concentrations greater than 0·5M. On the other hand, Evans and Pearson (*J. Amer. Chem. Soc.*, 1933, **55**, 1474) claimed that phenylmagnesium bromide was colloidal and that the ions concerned were rapidly and completely transferred to anode and cathode during electrolysis. Other evidence suggests that any association complexes present in solutions of Grignard compounds appear to be ionic and dissociate into simpler species at higher temperatures. From solubility measurements, Stewart and Ubbelohde (*J.*, 1949, 2649) obtained evidence for equilibria involving complex formation, probably of the type:

$$n\mathrm{RMgX} \rightleftharpoons \mathrm{Mg^{2+}} + [\mathrm{R}_n\mathrm{Mg}_{n-1}\mathrm{X}_n]^{2-}$$

In the present work association has been studied in a range of Grignard compounds, chiefly aromatic, in diethyl ether solution, to obtain information about polarisation bonds. Lowering of vapour pressure was followed by means of a tensimeter of special design, to permit of observations on the change of association with time and with temperature. The results now obtained confirm the existence of limited association of the Grignard compounds. When magnesium bromide is added to the solutions there is a notable increase of association, confirming the conclusions from solubility measurements. Association also increases with increase of concentration, and decreases somewhat with rise in temperature, showing that no large heat changes are involved. Equilibrium depends on too many variables to permit of calculation of exact heats of dissociation. If allowance is made for for differences in the temperature of measurement the present findings agree much better with Meisenheimer and Schlichenmaier's at the boiling point of the solutions than with the conclusions based on electrolytic studies on phenylmagnesium bromide.

Because of the powerful influence of magnesium bromide in promoting association, it proved difficult to distinguish any major influence of the molecular structure of the different aromatic radicals on the degree of complex formation. So far as comparisons could be made under similar conditions relative tendencies to promote association appear to lie in the sequences Br > Cl; *cyclo*hexyl > phenyl > *p*-tolyl > *o*-tolyl > *p*-methoxyphenyl.

Experimental

Preparation of the Aryl- and Alkyl-magnesium Bromides.—Methods described by Mackle and Ubbelohde (*J.*, **1948**, 1161) and Stewart and Ubbelohde (*J.*, **1949**, 2649) were used, the amounts of organic halide being adjusted to give the desired concentrations of Grignard solutions. Dry, oxygen-free nitrogen was used to protect all the ethereal solutions at every stage during preparation, transfer, and storage. In view of previous experience on the photosensitivity of Grignard compounds all work was carried out in the dark or in diffused light.

Magnesium bromide was prepared by reaction of magnesium and bromine under dry ether. The reaction was moderated by a cold-water bath. Pure nitrogen was then passed over the

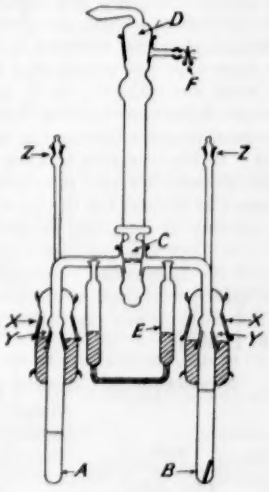


Fig. 1. *Tensimetric vapour-pressure apparatus.*

solution until only white crystals remained. The issuing nitrogen was passed into alcoholic silver nitrate solution; no precipitate resulted, indicating the absence of volatile organic bromo-compounds which might have resulted from attack on the ether. The crystals were redissolved in pure ether and this solution was filtered through glass wool. As previously reported (Menschutkin, *Z. anorg. Chem.*, **1906**—**1909**, **49**—**62**) the concentrated solution separates into two layers. The upper, water-white layer was used for vapour-pressure measurements and for addition of magnesium bromide to the other solutions studied. Estimation of bromide by Volhard's method and of magnesium gravimetrically as pyrophosphate gave a ratio of Mg : Br = 1·00 : 1·94 ± 0·03 (Calc. for $MgBr_2$, 1·00 : 2·00). This confirmed the conclusion obtained by the silver nitrate method that there was little or no attack on the ether, since reactions of the type

$$Mg + Br_2 + Et_2O \longrightarrow BrMg{\cdot}OEt + EtBr$$

would have increased the Mg : Br ratio above the theoretical value.

Differential Tensimetry.—In view of many difficulties encountered in obtaining reliable results with these labile ethereal solutions, the tensimeter is described in some detail (Fig. 1). All joints and taps except the B34 external joints *X* were well lubricated with starch–glycerol paste (Allen, Everett, and Penney, *Proc. Roy. Soc.*, 1952, *A*, **212**, 164) made by heating 8·25 g. of starch with 22 g. of glycerol under vacuum until a paste of the appropriate consistency resulted. The internal B14 joints *Y* on both tubes *A* and *B* were mercury-sealed by pouring dry mercury

through the A7 joints *Z*, fused to the cups. The B34 joints, isolating the mercury from the water of the thermostat, were well lubricated with silicone high-vacuum grease. The diameter (1 cm.) of the tubing of the manometer *E* was chosen to minimise surface tension effects, yet avoiding the use of exceptionally large quantities of mercury.

Pressure differences were measured with a travelling microscope, mounted on a fixed steel plate which had been grooved to form a geometrical clamp, giving the necessary degree of freedom.

About 5 ml. of pure, dry ether were distilled off from 10 ml. of the Grignard solution into tube *A*, under vacuum. Tube *A* was then transferred to the tensimeter, and 10 ml. of Grignard solution were transferred to tube *B*. Tubes *A* and *B* were then further protected from light by metal-foil coverings, and their contents were frozen in liquid air. The apparatus was then evacuated through tap *D* to a pressure of approximately 10^{-3} mm. Tap *D* was then closed, the screw clip *F* tightened, and the apparatus removed from the vacuum-train and allowed to warm to room temperature.

This freezing of the Grignard solutions and of the pure ether led to the squeezing out of much dissolved gas from the crystal lattices; bubbles were visible on melting. This degassing was considerably assisted by a few glass helices, previously placed in the two tubes. The two solutions were then again frozen and the apparatus re-evacuated, isolated as before from the vacuum train, and allowed to warm to about 15°. The Grignard solution was agitated thoroughly by a piece of soft iron enclosed in Pyrex glass, by use of a small strong magnet externally, and the apparatus was placed in a thermostat (±0·01°) with the three-way tap *C* closed. The water level was adjusted to be just below *C*. After the solutions had reached equilibrium the pressure difference was then noted. As check, solutions of naphthalene in ether gave a lowering of vapour pressure (which was steady) within ±0·5% of the value calculated for ideal 0·15M-solutions. In the complete absence of oxygen, vapour-pressure lowering due to the Grignard compounds likewise showed practically no drift at constant temperature. Drifts observed when oxygen was present are discussed below.

Analysis.—The content of Grignard reagent in the ethereal solutions was estimated by Gilman's acid titration. For this purpose a 10 ml. aliquot portion was pipetted out at the same time as filling of the tensimeter. To make sure changes of association were not due to decomposition, an aliquot portion was withdrawn from tube *A* at the end of a run and analysed in the same way. Total halide was also estimated by Volhard's method. Results are given in the second column of Table 1.

TABLE 1. *Association of Grignard reagents (complete absence of oxygen).*

R in RMgBr	Ratio, Halogen/Basicity	[RMgX] per 10 ml. ether (from basic titres) (milliequiv.)	Temp.	*i* uncorrected for side reactions	*i* corrected for side reactions
Phenyl	1·06 : 1·00	3·31	15·0°	1·85	1·97
	"	"	20·0	1·67	1·77
o-Tolyl	1·06 : 1·00	4·13	15·0	1·32	1·38
	"	"	20·0	1·33	1·39
p-Tolyl	1·20 : 1·00	2·10	15·0	1·27	1·58
	1·04 : 1·00	3·68	15·0	1·56	1·80
	"	5·66	15·0	1·71	2·03
	—	"	20·0	1·65	1·82
p-Methoxyphenyl	1·13 : 1·00	3·27	15·0	1·08	1·10
	—	—	20·0	1·00	1·03
*cyclo*Hexyl	1·21 : 1·00	1·89	15·0	1·76	2·29
	1·25 : 1·00	3·24	15·0	2·09	2·93
	—	"	20·0	2·05	2·94
	1·25 : 1·00	6·69	15·0	2·60	4·14
	"	"	20·0	2·19	3·33
*cyclo*Hexyl (chloride)	1·09 : 1·00	5·51	15·0	1·20	1·28
	"	"	20·0	1·20	1·29
$MgBr_2$	—	0·71	20·0	1·05	—

Departure of the ratio halogen/basic titre from 1·00 indicates that in addition to the normal Grignard reaction Mg + RX ⟶ RMgX side reactions (cf. Meisenheimer and Schlichenmaier, *Ber.*, 1928, **61**, 720) of the type

$$Mg + 2RX \longrightarrow R_2 + MgX_2 \quad \text{(Würtz)}$$

and

$$Mg + 2RX \longrightarrow RH + R'' + MgX_2 \quad \text{(disproportionation)}$$

had occurred to some extent. When it was necessary to correct for these side reactions in subsequent molecular-weight determinations, the Würtz reaction was assumed to predominate, in accordance with general experience. As a result of solubility measurements (Stewart and Ubbelohde, *loc. cit.*) and other experiments quoted below, the MgX_2 in excess of the ratio 1·00 was taken to be incorporated into the association complex. Any uncertainty arising from these assumptions is serious only for *cyclo*hexylmagnesium bromide.

Mean Molecular Weights.—Observed lowerings of the vapour pressure by Δp (mm.) can conveniently be combined with the known vapour pressures p of pure diethyl ether at the same temperatures (taken from the International Critical Tables) by assuming the formal relation

$$\Delta p/p = n/(N + n) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where n is the number of moles of solute and N the number of moles of ether.

If n = number of moles of complex per 10 ml. of ether calculated from (1) and n_B = number of moles expected on the basis of the Gilman analyses, the formula weight being assumed to be the same as the molecular weight, then

$$i = n_B/n \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

Values of i uncorrected for any side reactions are given in Table 1. Values found by assuming Würtz side reactions and incorporation of the MgX_2 into the association complex are calculated by subtracting the lowering of vapour pressure $\Delta p'$ due to the R_2 molecules, from the total, and then calculating the number of moles n' from the equation

$$(\Delta p - \Delta p')/p = n'/(N + n') \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

and

$$i_{corr.} = n_T/n' \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

where n_T = number of moles of complex expected on the basis of the Gilman titration plus number of moles of magnesium bromide produced by Würtz reaction. The following is a typical calculation for the extreme case of *cyclo*hexylmagnesium bromide.

The concentrations (per 10 ml.) of the Grignard reagent (6·69 milliequiv.) and of magnesium bromide (8·36 milliequiv.) found differ by 1·67 milliequiv. or 0·84 mmoles. Thus n_T = 6·69 + 0·84 = 7·53 mmoles, and the Würtz reaction has produced 0·84 mmoles of both di*cyclo*hexyl and magnesium bromide. The vapour pressure of diethyl ether being 360·7 mm. and the number of moles of ether, N, in 10 ml. of this solution being 0·0991, at 15°, the di*cyclo*hexyl will, by Raoult's law, produce a lowering of the vapour pressure, $\Delta p'$, given by

$$\Delta p' = 360{\cdot}7 \times 0{\cdot}84 \times 10^{-3}/(0{\cdot}84 \times 10^{-3} + 0{\cdot}0991) = 3{\cdot}01 \text{ mm.}$$

The lowering due to the Grignard complex is thus $\Delta p - \Delta p'$, corresponding to n' moles of complex and N of ether, and Δp is found experimentally to be 9·49. Equation (3), therefore, becomes $(9{\cdot}49 - 3{\cdot}01)/360{\cdot}7 = n'/(n' + 0{\cdot}0991)$, from which n' = 1·81 mmoles per 10 ml. and, from equation (4), $i_{corr.} = 7{\cdot}53/1{\cdot}81 = 4{\cdot}14$. This correction leads to somewhat higher values of i, as shown in Table 1.

Addition of Excess of Magnesium Bromide.—Because of the marked effect of the magnesium bromide produced in side reactions on the degree of association, it was desirable to obtain some quantitative measure of changes due to variations in concentration of magnesium bromide.

TABLE 2. *Effect of magnesium bromide on the association of Grignard compounds at* 15°.

R in RMgBr	Concn. (mmoles/ per 10 ml. of ether)	Halogen/ basicity	i uncorr.	R in RMgBr	Concn. (mmoles/ per 10 ml. of ether)	Halogen/ basicity	i uncorr.
Phenyl	3·31	1·06	1·90	*p*-Methoxyphenyl	3·27	1·00	1·10
	2·69	1·20	2·22		2·10	1·20	1·30

The two systems selected had quite different concentrations of magnesium bromide originally, and were brought to approximately the same halogen/basicity titre by the addition of pure magnesium bromide dissolved in ether. Results were as in Table 2; the upper line gives the parameters of the solution as prepared in the formation of the Grignard compound, the lower the solution after addition of magnesium bromide.

Association in the Presence of Small Amounts of Oxygen.—The experimental evidence to be described differs from that on the more extensive attack by this gas on Grignard solutions

(Meisenheimer, *Ber.*, **1928**, **61**, 708), in that much less oxygen was involved in our experiments. The influence of oxygen now observed may even be catalytic. Two principal types of observation were made: (i) If the solutions of aromatic Grignard compounds were prepared and handled throughout under nitrogen rigorously freed from oxygen, they could be frozen to give white crystals and remelted to give identical products. But if the nitrogen contained as little as 2% of oxygen, even when the solutions were exposed to this gas for only a few minutes, a heavy yellow oil separated on freezing. After warming, this could only be redispersed after considerable agitation. Separate analyses of the two layers showed an enhancement of the halogen/basicity ratio in the oil. This would hardly be the case if this polymer incorporated Mg–OR linkages (Meisenheimer). Further discussion of this polymerisation is deferred. Comparisons of the vapour pressures before and after freezing out of the oil showed very little change due to its removal, showing that its molecular weight was very considerably higher than that of the ordinary association complex.

TABLE 3*A*. *Effects of oxygen on the composition of the association complexes.*

R in RMgBr	Halogen/basicity		R in RMgBr	Halogen/basicity	
o-Tolyl	Original overall	1·03 : 1·00	*p*-Tolyl	Original overall	1·04 : 1·00
	In upper layer after freezing	0·92 : 1·00		In upper layer after freezing	1·00 : 1·00
	In oil after freezing	1·25 : 1·00		In oil after freezing	1·19 : 1·00

Storage of Grignard solutions for 24 hr. under nitrogen in flasks fitted with ungreased standard ground stoppers led to the separation of oil after freezing. When a positive pressure of nitrogen was maintained, with ungreased stoppers, no oil was formed. *cyclo*Hexylmagnesium bromide (and magnesium dibromide) showed no tendency to polymerise in this way. *cyclo*-Hexylmagnesium bromide solutions froze to a clear glass whether exposed to oxygen or not.

(ii) If solutions of Grignard compounds were exposed for a brief time to diluted oxygen, and were then examined in the tensimeter, the vapour pressure was much less steady and tended to drift for as much as 100 hr. *cyclo*Hexylmagnesium bromide showed no drift. Ultimately a markedly higher degree of overall association was observed than in the absence of oxygen. This can be seen from Table 3*B*, which should be compared with Table 1.

TABLE 3*B*. *Association in the presence of small quantities of oxygen.*

R in RMgBr	Concn., mmoles/ per 10 ml.	Temp.	$i_{\text{uncorr.}}$	R in RMgBr	Concn., mmoles/ per 10 ml.	Temp.	$i_{\text{uncorr.}}$
Phenyl	4·20	15·0°	5·98	*p*-Tolyl	1·87	15·0°	3·88
						20·0	

DISCUSSION

Inspection of the i values in Table 1 makes it evident that these Grignard compounds are associated to a moderate extent in ether. There is an increase in association with increase of concentration for example in the *cyclo*hexyl or *p*-tolyl compounds; an overall picture is obtainable from Fig. 2. Increase of temperature decreases association to some extent for *cyclo*hexyl-, phenyl-, *p*-tolyl-, and *p*-methoxyphenyl-magnesium bromide, but has little effect on *o*-tolylmagnesium bromide or on *cyclo*hexylmagnesium chloride. Heats of dissociation appear to be small. Exact calculation from the van't Hoff isochore is hampered by the number of variables which influence the degree of association. A large number of experiments would be required to establish the precise equilibrium constants at different temperatures.

As shown in Table 2, i for phenylmagnesium bromide is raised from 1·90 to 2·22 by adding magnesium bromide equivalent to the amount present in *cyclo*hexylmagnesium bromide. At corresponding concentrations of magnesium bromide the i value for the *cyclo*hexyl compound is still appreciably greater (2·70), while *p*-methoxyphenylmagnesium bromide even with a halogen/basic titre ratio raised to 1·20 is still the least associated bromide. Differences between the organic radicals discussed below are thus somewhat reduced but are not wiped out when allowance is made for the magnesium bromide present. Magnesium bromide has $i = 1{\cdot}05$ referred to undissociated magnesium bromide. Apart from the possibility that it exists very largely in undissociated form in ethereal solution,

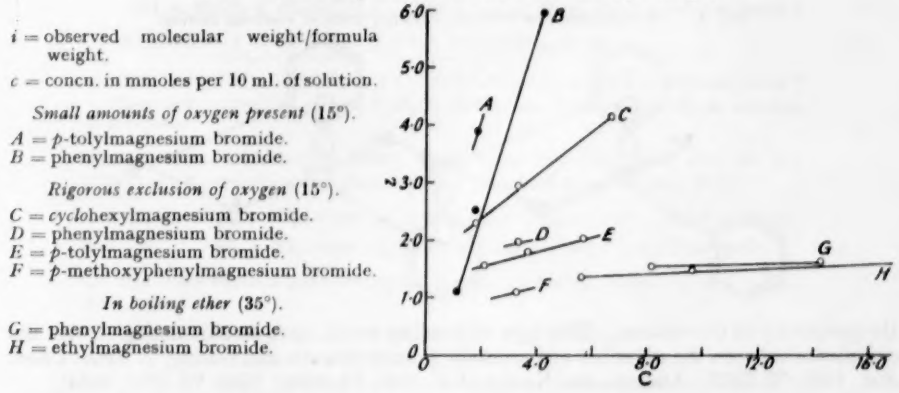
it could also be present mainly as $[Mg,nEt_2O]^{2+}[^{Br}_{Br}>Mg<^{Br}_{Br}]^{2-}$ (cf. Meisenheimer and Schlichenmeier, *loc. cit.*) but in the presence of excess of Grignard compound which forms complexes with magnesium bromide any correction for this effect may be neglected.

Detailed Effects of the Structure of R *on the Degree of Association.*—Further interpretation of the results requires additional assumptions which seem reasonable but are not yet fully substantiated. On the basis of the work of Evans and his colleagues, it seems likely that the Grignard compounds must be written in the form $Mg^{2+}[Mg_{r-1}R_rX_r]^{2-}$, possibly with some ether co-ordinated with the ions. At present the values of r are not known. Indeed, it seems likely that a cascade of equilibria is present, of the type

$$[Mg_{r+1}R_rX_r]^{2-} \rightleftharpoons RMgX + [Mg_rR_{r-1}X_{r-1}]^{2-}$$
$$[Mg_rR_{r-1}X_{r-1}]^{2-} \rightleftharpoons RMgX + [Mg_{r-1}R_{r-2}X_{r-2}]^{2-}$$

Furthermore, when excess of magnesium bromide is added it is readily incorporated into the complexes, facilitating the building-up of larger values of r. If, as a simplifying

FIG. 2. *Variation of association with concentration for* RMgBr.



approximation, only a single species of complex anion is assumed to be present, the calculated values of r change with concentration, and with the nature of R, as shown in Table 4. The series refer to the same experiments as in Table 1. $r = 2i_{corr.}$

TABLE 4. *Apparent size,* r, *of complex anions in Grignard compounds,* RMgBr.

R	r	Temp.	R	r	Temp.	R	r	Temp.
Phenyl	3·94	15·0°	*p*-Tolyl	3·16	15·0°	*cyclo*Hexyl	4·58	15·0°
	3·54	20·0		3·60	15·0		5·86	15·0
				4·06	15·0		5·88	20·0
o-Tolyl	2·76	15·0		3·64	20·0		8·28	15·0
	2·78	20·0					6·66	20·0
			p-Methoxy-	2·20	15·0		2·56	15·0
			phenyl	2·06	20·0		2·58	20·0

Except in the extreme case of *cyclo*hexylmagnesium bromide, differences in the halogen/basicity ratio are not sufficiently large (cf. Table 2) to have major influence on the values of r, and may provisionally be disregarded. When values of r for the different R radicals are compared, it seems safe to say that these promote association in the sequence *cyclo*hexyl > phenyl > *p*-tolyl > *o*-tolyl > *p*-methoxyphenyl. The origin of the association forces present is not definitely known, so that only brief reference will be made to some of the possibilities.

(i) In principle, all the aromatic radicals can act as acceptor groups and form polarisation bonds with the halogens. The direction of the electron displacement in the dotted polarisation bond is shown by the arrow in Fig. 3. For this kind of association, which resembles that in potassium graphite (McDonnell, Pink, and Ubbelohde, *J.*, 1951, 191) and

in potassium anthracene (Holmes-Walker, and Ubbelohde, *J.*, 1954, 720), substituents in the aromatic group which are electron donors should reduce the tendency to form association bonds between the bromide ion and the acceptor aromatic group. Roughly speaking, this is what is found, though steric effects probably also operate. This polarisation bonding would be stronger for Br^- than for Cl^- which is again as found. Recently a crystalline compound between bromine and perylene has been described (Akamatu, Inokuchi, and Matsunaga, *Nature*, 1954, **173**, 168) in which perylene appears to be the electron acceptor.

(ii) The aromatic groups might act as donor groups, through an overlap of their π-orbitals with empty orbitals of the magnesium, such as an sp^3-hybridised tetrahedral set (Fig. 4). Overlap of this kind could be stabilised by the formation of a complex anion which increases

FIG. 3. *Phenylmagnesium bromide complex with possible polarisation bonding.*

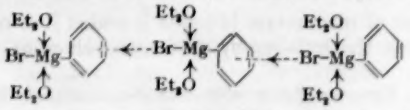
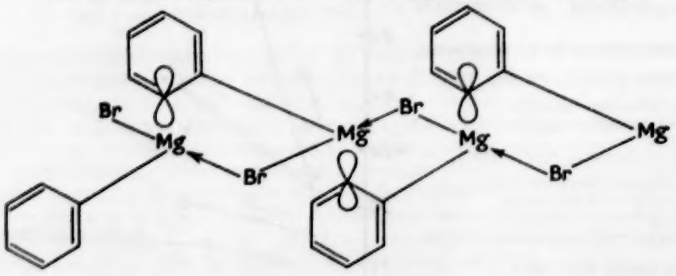


FIG. 4. *Phenylmagnesium bromide, showing possible π-orbital overlap.*



the symmetry of the system. This type of bonding would have certain analogies with the complexes between the silver ion and aromatic groups (Rundle and Goring, *J. Amer. Chem. Soc.*, 1950, **72**, 5337; Andrews and Keefer, *ibid.*, 1949, **71**, 3644; 1950, **72**, 3113, 5034).

Bonding in benzene complexes such as C_6H_6,Al_2Br_6, C_6H_6,Al_2I_6, which are stated to exist in solution (Eley and King, *J.*, 1952, 4972) has been represented by the two canonical structures :

(I) C_6H_6,Al_2Br_6 $\qquad\qquad$ $C_6H_6^+,Al_2Br_6^-$ (II)

The bonding in (I) and (II) may involve aromatic donor groups with electron interaction with the aluminium. Or there may be donation of *d*-electrons from bromine to the anti-bonding orbitals of the aromatic group acting as electron acceptor (Dewar, *Bull. Soc. chim.*, 1951, **18**, 79C; Eley and King, *loc. cit.*). These alternative suggestions have analogies with possibilities (i) and (ii) above.

(iii) The *cyclo*hexyl group which shows tendencies to promote association is incapable of forming either type of bonding described above for aromatic systems. Unless the association is to be entirely attributed to the halogen groups, *cyclo*hexyl must form overlap bonds of some kind with empty orbitals of the magnesium atoms, but their nature is as yet obscure.

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A Thermochemical Evaluation of Bond Strengths in Some Carbon Compounds. Part III. Bond Strengths based on the Reactions: (a)* $Ph{\cdot}CH_2I + HI \longrightarrow Ph{\cdot}CH_3 + I_2$ *and (b)* $PhI + HI \longrightarrow PhH + I_2$.

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Methods described in Part II * have been used to determine heat changes in the reactions:

(A) (1) $Ph{\cdot}CH_2{\cdot}MgCl + I_2 \longrightarrow Ph{\cdot}CH_2I + MgICl$; $Q_1 = -105{\cdot}9 \pm 0{\cdot}8$ kcal./mole.

(2) $Ph{\cdot}CH_2{\cdot}MgCl + HI \longrightarrow Ph{\cdot}CH_3 + MgICl$; $Q_2 = -113{\cdot}7 \pm 0{\cdot}7$ kcal./mole.

(all in *p*-xylene solution)

(B) (3) $\underbrace{PhMgBr + 505{\cdot}2\ C_7H_8O}_{} + \underbrace{I_2 + 182{\cdot}7\ C_7H_{16}}_{} \longrightarrow$

$PhI + MgIBr + 505{\cdot}2\ C_7H_8O + 182{\cdot}7\ C_7H_{16}$; $Q_3 = 123{\cdot}9 \pm 1{\cdot}0$ kcal./mole.†

(4) $\underbrace{PhMgBr + 505{\cdot}2\ C_7H_8O}_{} + \underbrace{HI + 182{\cdot}7\ C_7H_{16}}_{} \longrightarrow$

$PhH + MgIBr + 505{\cdot}2\ C_7H_8O + 182{\cdot}7\ C_7H_{16}$; $Q_4 = 114{\cdot}3 \pm 0{\cdot}8$ kcal./mole.†

(Grignard reagent in anisole, C_7H_8O; iodine and hydrogen iodide in solution in *n*-heptane)

Known heats of reaction being used, these reactions give rise to the important thermochemical quantities (at standard pressure and 25°):

(6) $Ph{\cdot}CH_2I_g + HI_g \longrightarrow I_{2,g} + Ph{\cdot}CH_{3,g}$; $-Q_6 = +1{\cdot}0 \pm 1{\cdot}3$ kcal./mole

and (10) $PhI_g + HI_g \longrightarrow I_{2,g} + PhH$; $-Q_{10} = -5{\cdot}2 \pm 1{\cdot}4$ kcal./mole.

On this basis various bond strengths can be calculated, including new values for:

$$D(Ph{\cdot}CH_2{-}H) - D(Ph{\cdot}CH_2{-}I) = 34{\cdot}3 \pm 1{\cdot}3 \text{ kcal./mole}$$

$$D(Ph{\cdot}CH_2{-}I) = 43{\cdot}2 \pm 1{\cdot}8 \text{ kcal./mole}$$

$$D(Ph{-}H) - D(Ph{-}I) = 40{\cdot}5 \pm 1{\cdot}6 \text{ kcal./mole}$$

and

$$D(Ph - I) = 60{\cdot}9 \pm 1{\cdot}8 \text{ kcal./mole}$$

Differences between the corresponding disruption energies for the phenyl and the benzyl compounds are compared with those for methyl iodide and are discussed in terms of the electronic structures. (Here the Q and q symbols are identical with ΔH.)

For development of the physical chemistry of aromatic systems, there are still only few data on bond disruption energies from which quantitative information can be derived about inductive and mesomeric effects in the ground states of the molecules. Grignard-reaction calorimetry seemed likely to open up an extensive range of interesting bond data on aromatic systems, and has therefore been investigated as described below. The chief difficulty in this method of measuring disruption energies in important aromatic compounds was found to lie in the chemistry of the Grignard reactions. It proved unexpectedly difficult to establish conditions where useful stoicheiometric reactions took place. Whilst the general reason for these difficulties appears to be the long life of some of the free radicals produced as reaction intermediates, the present paper gives details only for the solvents and concentration ranges which gave reactions usable in chemical calorimetry. Methods described below give new bond data for a significant pair of aromatic compounds, and open up the field for further developments. The significance of the wide range of reactions discovered in which the stoicheiometry is different is being further studied.

* Part II, *J.*, 1952, 415.

† These values include a large heat-absorption term resulting from the mixing of anisole and heptane in the amounts indicated in the equations. This term cancels out in the subsequent thermochemical equations.

Experimental

Preparation of Solutions of Reagents.—Solutions of the Grignard reagents, of hydrogen iodide, and of iodine were prepared as in Part II (*loc. cit.*). Benzyl chloride was used instead of the bromides and iodides employed hitherto, because it was found to give more favourable preparations for the present purpose. Commercial benzyl chloride and phenyl bromide were purified by refluxing them *in vacuo* over fresh calcium turnings and then distilling them at reduced pressure. Benzylmagnesium chloride was prepared in pure diethyl ether and diluted with pure *p*-xylene so that the resulting 0·08M-Grignard solution contained approximately 1% v/v of diethyl ether.

Phenylmagnesium bromide was prepared in a similar manner but was diluted with pure anisole instead of *p*-xylene. The resultant 0·08M-solution of Grignard reagent contained a similar proportion of ether. For reactions involving phenylmagnesium bromide *n*-heptane was used as solvent for the iodine and hydrogen iodide. This solvent was purified by prolonged storage over fuming sulphuric acid to remove unsaturated materials, then shaken with 10% potassium hydroxide solution to remove traces of acid, dried by prolonged storage over potassium hydroxide pellets, and refluxed over sodium wire, over which it was fractionally distilled; the fraction of b. p. 97—97·5° was used.

Stoicheiometry of the Reactions.—Tables 1 and 2 give typical examples of the reactions of iodine and hydrogen iodide with phenylmagnesium bromide and benzylmagnesium chloride.

Table 1. *Mean of ten iodine reactions.*

	I_2 solution (M)	Grignard solution (M)	Grignard reagent orig. (mmole)	reacted (mmole)	I_2 reacted (mmole)
$Ph{\cdot}CH_2{\cdot}MgCl$	0·02	0·087	1·740	0·256	0·252
PhMgBr	0·036	0·069	1·379	0·359	0·362

Table 2. *Mean of ten hydrogen iodide reactions.*

	HI solution (M)	Grignard solution (M)	Grignard reagent orig. (mmole)	reacted (mmole)	HI reacted (mmole)
$Ph{\cdot}CH_2{\cdot}MgCl$	0·018	0·087	0·740	0·514	0·510
PhMgBr	0·036	0·069	1·379	0·353	0·357

The reactions of iodine and hydrogen iodide with benzylmagnesium chloride proceeded smoothly in *p*-xylene (cf. Part II) and resulted in quantitative conversion of benzylmagnesium chloride into benzyl iodide and toluene respectively, according to the equations:

$$(a)\quad Ph{\cdot}CH_2{\cdot}MgCl + I_2 \longrightarrow Ph{\cdot}CH_2I + MgICl \qquad (1)$$

$$(b)\quad Ph{\cdot}CH_2{\cdot}MgCl + HI \longrightarrow Ph{\cdot}CH_3 + MgICl \qquad (2)$$

(all in *p*-xylene)

On the other hand the reactions involving phenylmagnesium bromide did not give quantitative stoicheiometry in *p*-xylene. Therefore the stoicheiometry of these reactions was investigated in a series of pure and mixed solvents, including diethyl ether, ethyl tetrahydropyran-2-yl ether, diphenyl ether containing diphenyl, anisole, and an anisole–heptane mixture. The general trend of reactions in *p*-xylene supported the working hypothesis that the mechanism of the desired reaction was ionic. In the case of phenylmagnesium bromide a solvent more polar than *p*-xylene was indicated in order to suppress free-radical reactions. Finally, anisole containing about 1% of diethyl ether was chosen as solvent for the Grignard reagent. Ethers are unsuitable as solvents for hydrogen iodide, when there is prolonged contact. To balance the thermal cycles, *n*-heptane was used for both iodine and hydrogen iodide. Under these conditions the reactions followed the equations:

$$(a)\quad \underset{\text{(anisole)}}{PhMgBr} + \underset{\text{(heptane)}}{I_2} \longrightarrow \underset{\text{(anisole–heptane)}}{PhI} + MgIBr \qquad (3)$$

$$(b)\quad \underset{\text{(anisole)}}{PhMgBr} + \underset{\text{(heptane)}}{HI} \longrightarrow \underset{\text{(anisole–heptane)}}{PhH} + MgIBr \qquad (4)$$

Typical examples of the stoicheiometry in these solvents are quoted in the above Tables. Various subsidiary thermal quantities were required to complete the thermochemical cycles

below. Some of these were obtained from the literature but the following were determined experimentally :

Heat of vaporisation of HI *from* n*-heptane solution.* This was evaluated by direct determination of the equilibrium concentrations of hydrogen iodide vapour above the solution at four different temperatures (for method see Part II).

Heat of vaporisation of benzyl iodide from the Grignard solutions. A procedure corresponding to that for hydrogen iodide was adopted, with alcoholic silver nitrate as the analytical reagent.

The Constant-pressure Calorimeter.—For the measurement of the heat changes in the reactions involving benzylmagnesium chloride the constant-pressure calorimeter described in Part II was used. However, a modified form of this calorimeter was employed for the reactions of phenylmagnesium bromide. The main modifications were a reduction of about 30% in the size of the constant-temperature jacket, and a closer control of temperature at 25° ± 0·001° in the jacket by means of a toluene regulator with a " Sunvic " proportionating head. The toluene (130 ml.) was contained in two glass bulbs diametrically opposed in the block. The remaining procedures and precautions, including the calibration of the calorimeter, were essentially as recorded in Part II.

Results

The following heats of reaction were calculated from the observations for the reactions involving benzylmagnesium chloride (1 calorie = 4·1833 × 10^7 ergs. N.B. : throughout this paper, as in Parts I and II, the Q and q symbols are identical with ΔH, *not* $-\Delta H$).

$$\underset{0\cdot087\text{M}}{\text{Ph}\cdot\text{CH}_2\cdot\text{MgCl}} + \underset{0\cdot018\text{M}}{\text{HI}} \longrightarrow \underset{0\cdot00578\text{M}}{\text{Ph}\cdot\text{CH}_3} + \underset{0\cdot00578\text{M}}{\text{MgICl}};\ Q_2 = -113\cdot7 \pm 0\cdot7 \text{ kcal./mole} \quad . \quad (2)$$

$$\underset{0\cdot087\text{M}}{\text{Ph}\cdot\text{CH}_2\cdot\text{MgCl}} + \underset{0\cdot02\text{M}}{\text{I}_2} \longrightarrow \underset{0\cdot0065\text{M}}{\text{Ph}\cdot\text{CH}_2\text{I}} + \underset{0\cdot0065\text{M}}{\text{MgICl}};\ Q_1 = -105\cdot9 \pm 0\cdot8 \text{ kcal./mole} \quad . \quad (1)$$

Combination of equations (1) and (2), neglecting small differences in molality, gives :

$$\underset{0\cdot018\text{M}}{\text{HI}} + \underset{0\cdot0065\text{M}}{\text{Ph}\cdot\text{CH}_2\text{I}} \longrightarrow \underset{0\cdot00578\text{M}}{\text{Ph}\cdot\text{CH}_3} + \underset{0\cdot02\text{M}}{\text{I}_2};\ Q_5 = -7\cdot8 \pm 1\cdot1 \text{ kcal./mole} \quad . \quad . \quad . \quad (5)$$

(all in *p*-xylene)

The heat of a similar reaction in the gaseous phase can be arrived at from the cyclic process :

$$\underset{0\cdot0065\text{M}}{\text{Ph}\cdot\text{CH}_2\text{I}} + \underset{0\cdot018\text{M}}{\text{HI}} \xrightarrow{Q_5} \underset{0\cdot00578\text{M}}{\text{Ph}\cdot\text{CH}_3} + \underset{0\cdot02\text{M}}{\text{I}_2};\ Q_5 = -7\cdot8 \pm 1\cdot1 \text{ kcal./mole} \quad . \quad . \quad (5)$$

$$\uparrow q_1 \qquad \uparrow q_2 \qquad \downarrow q_3 \qquad \downarrow q_4$$

$$\text{Ph}\cdot\text{CH}_2\text{I}_g + \text{HI}_g \xleftarrow{Q_6} \text{Ph}\cdot\text{CH}_{3,g} + \text{I}_{2,g};\ Q_6 = -1\cdot0 \pm 1\cdot3 \text{ kcal./mole} \quad . \quad . \quad (6)$$

The heat of the gaseous reaction (6) can be calculated from the heat terms indicated in the cycle :

$$Q_6 = -Q_5 - (q_1 + q_2 + q_3 + q_4) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

In equation (7) the subsidiary thermal quantities were evaluated as described in the following paragraphs :

(i) q_1 was determined from directly measured partial pressures of benzyl iodide over the solutions corresponding to the end-concentrations of the calorimetric reactions, at different temperatures. Partial pressures found over the solution represented in equation (1) were 0·255 mm. at 298° K, 0·287 mm. at 303° K, and 0·419 mm. at 308° K. From the slope of the plot of log p against $1/T$ it is calculated that $q_1 = -8\cdot9 \pm 0\cdot5$ kcal./mole.

(ii) $\text{HI}_g \longrightarrow \text{HI}_{p\text{-xylene sol.}}$: $q_2 = -3\cdot0 \pm 0\cdot2$ kcal./mole. For the determination of this quantity see Part II.

(iii) $q_3 = (\Delta H_1 + \Delta H_2) = 9\cdot1 \pm 0\cdot5$ kcal./mole, where, for $\text{Ph}\cdot\text{CH}_{3\,p\text{-xylene sol.}} \longrightarrow \text{Ph}\cdot\text{CH}_{3\,\text{liquid}}$, ΔH_1 = zero (determined experimentally); and the heat of vaporisation, $\text{Ph}\cdot\text{CH}_{3\,\text{liquid}} \longrightarrow \text{Ph}\cdot\text{CH}_{3\,\text{gas}}$, $\Delta H_2 = 9\cdot1 \pm 0\cdot5$ kcal./mole (Pitzer and Scott, *J. Amer. Chem. Soc.*, **1943**, **65**, 803).

(iv) $q_4 = +11\cdot6 \pm 0\cdot7$ kcal./mole (see Part II).

Solubilities (S; g./100 g. of solution) of crystalline iodine in *p*-xylene were redetermined: 15·43 at 292·92° K; 16·50 at 296·86° K; 17·55 at 300·04° K. From the plot of log S against $1/T$ a new value of the heat of solution (ΔH_4 of Part II) was found:

$$I_{2,\,cryst.} + p\text{-xylene} \longrightarrow I_{2,\,p\text{-xylene sol.}} + 3{\cdot}3 \pm 0{\cdot}2 \text{ kcal./mole.}$$

For the reactions involving phenylmagnesium bromide the following heats of reaction were calculated from the observations:

$$\underbrace{PhMgBr + 505{\cdot}2\,C_7H_8O}_{} + \underbrace{HI + 182{\cdot}7\,C_7H_{16}}_{} \longrightarrow$$

$$PhH + MgIBr + 505{\cdot}2\,C_7H_8O + 182{\cdot}7\,C_7H_{16};\quad Q_3 = 114{\cdot}3 \pm 0{\cdot}8 \text{ kcal./mole} \quad . \quad (3)$$

$$\underbrace{PhMgBr + 505{\cdot}2\,C_7H_8O}_{} + \underbrace{I_2 + 182{\cdot}7\,C_7H_{16}}_{} \longrightarrow$$

$$PhI + MgIBr + 505{\cdot}2\,C_7H_8O + 182{\cdot}7\,C_7H_{16};\quad Q_4 = 123{\cdot}9 \pm 1{\cdot}0 \text{ kcal./mole} \quad . \quad . \quad . \quad (4)$$

[mean probable error in individual results from five independent experiments in both (3) and (4)]

Combination of equations (3) and (4) gives:

$$\underset{\substack{0{\cdot}036\text{M}\\ \text{in heptane}}}{HI} + \underset{\substack{0{\cdot}012\text{M}\\ \text{in anisole}\\ \text{–heptane}}}{PhI} \longrightarrow \underset{\substack{0{\cdot}012\text{M}\\ \text{in anisole}\\ \text{–heptane}}}{PhH} + \underset{\substack{0{\cdot}036\text{M}\\ \text{in heptane}}}{I_2} \quad ;\ Q_9 = -9{\cdot}6 \pm 1{\cdot}4 \text{ kcal./mole} \quad (9)$$

The heat of a similar reaction in the gaseous phase can be arrived at from the cyclic process:

$$\underset{\substack{0{\cdot}012\text{M}\\ \text{in anisole}\\ \text{–heptane}}}{PhI} + \underset{\substack{0{\cdot}036\text{M}\\ \text{in heptane}}}{HI} \xrightarrow{Q_9} \underset{\substack{0{\cdot}012\text{M}\\ \text{in anisole}\\ \text{–heptane}}}{PhH} + \underset{\substack{0{\cdot}036\text{M}\\ \text{in heptane}}}{I_2} \quad ;\ Q_9 = -9{\cdot}6 \pm 1{\cdot}4 \text{ kcal./mole}$$

$$\uparrow q_6 \qquad \uparrow q_5 \qquad \downarrow q_7 \qquad \downarrow q_8$$

$$PhI_{gas} + HI_{gas} \xleftarrow{Q_{10}} PhH_{gas} + I_{2\,gas} \quad ;\ Q_{10} = +5{\cdot}2 \pm 1{\cdot}4 \text{ kcal./mole}$$

The heat of the gaseous reaction (10) (page 115) can be calculated from the heat terms indicated in the cycle:

$$Q_{10} = -Q_9 - (q_5 + q_6 + q_7 + q_8) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (11)$$

In equation 11 the subsidiary thermal quantities were evaluated as described in the following paragraphs:

(i) $q_5 = (\Delta H_3 + \Delta H_4) = -9{\cdot}5 \pm 0{\cdot}2$ kcal./mole, where, for $PhI_g \longrightarrow PhI_l$, $\Delta H_3 = -9{\cdot}5 \pm 0{\cdot}2$ kcal./mole. (Zil'berman-Granovskaya and Shugsam, *J. Phys. Chem. U.S.S.R.*, 1940, **14**, 1004); and, for $PhI_l \longrightarrow PhI_{\text{products of reaction (4)}}$, $\Delta H_4 =$ zero (determined experimentally).

(ii) $q_6 = -3{\cdot}4 \pm 0{\cdot}2$ kcal./mole. This quantity was determined by the method described in Part II. The values for the partial pressure (mm.) of hydrogen iodide over heptane at the specified temperatures are: 19·75 at 294·95° K, 20·63 at 296·85° K, 21·04 at 299·06° K, 22·27 at 301·30° K. From the slope of the line obtained when the log of the partial pressure of hydrogen iodide was plotted against $1/T$, the heat term q_6 was calculated.

(iii) $q_7 = (\Delta H_5 + \Delta H_6) = +8{\cdot}3 \pm 0{\cdot}2$ kcal./mole, where, for $PhH_{\text{products of reaction (3)}} \longrightarrow PhH_l$, $\Delta H_5 =$ zero (determined directly in the calorimeter); and, for $PhH_{liquid} \longrightarrow PhH_{gas}$, $\Delta H_6 = +8{\cdot}3 \pm 0{\cdot}2$ kcal./mole (Timmermans, "Physico-Chemical Constants of Pure Organic Substances," Elsevier, Amsterdam, 1951).

(iv) $q_8 = \Delta H_7 + \Delta H_8 = +9{\cdot}0 \pm 0{\cdot}3$ kcal./mole, where for $I_{2,\,heptane} \longrightarrow I_{2,\,cryst.}$, $\Delta H_7 = -5{\cdot}9 \pm 0{\cdot}2$ kcal./mole (Semb, *J. Amer. Pharm. Assoc.*, 1935, **24**, 547); and for $I_{2,\,cryst.} \longrightarrow I_{2,\,gas}$, $\Delta H_8 = +14{\cdot}9 \pm 0{\cdot}2$ kcal./mole (Bichowsky and Rossini, "Thermochemistry of Chemical Substances," Rheinhold Publ. Corpn., New York, 1936). Insertion of these values into equation (11) gives $Q_{10} = 5{\cdot}2 \pm 1{\cdot}4$ kcal./mole.

The heat of mixing of anisole and *n*-heptane in the proportions present during the reactions (3) and (4) was determined directly in the calorimeter. Although this value was not required for the calculations involved in the thermochemical cycle above it was considered advisable to know this term as its magnitude affected appreciably the measured heats of reactions (3) and (4). It was found that, for $505{\cdot}2\,C_7H_8O + 182{\cdot}7\,C_7H_{16} \longrightarrow$ Mixture, $\Delta H_9 = 192{\cdot}6 \pm 1{\cdot}4$ kcal./mole.

Discussion

The value $Q_6 = -1{\cdot}15 \pm 1{\cdot}29$ kcal. may be used in conjunction with known bond-dissociation energies. For example, equation (6) can be transformed into

$$D(\text{Ph}\cdot\text{CH}_3\text{–I}) + D(\text{H–I}) \longrightarrow D(\text{Ph}\cdot\text{CH}_3\text{–H}) + D(\text{I–I});\ -Q_6 = +1{\cdot}0 \pm 1{\cdot}3 \text{ kcal./mole}$$

Combining this with the accurately known values (at 291° K) for D(H–I) = 71·6 ± 0·2 kcal. and for D(I–I) = 36·3 ± 0·2 kcal. (Bichowsky and Rossini, *op. cit.*) gives the bond substitution energy I for H in toluene :

$$D(\text{Ph}\cdot\text{CH}_3\text{–H}) - D(\text{Ph}\cdot\text{CH}_3\text{–I}) = 34{\cdot}3 \pm 1{\cdot}3 \text{ kcal./mole} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

In view of the uncertainties of bond-dissociation energies, stating the result in this form seems preferable at the present time. However, if the result (8) is combined with the known value $D(\text{Ph}\cdot\text{CH}_2\text{–H}) = 77{\cdot}5 \pm 1{\cdot}3$ kcal./mole (Szwarc, *J. Chem. Phys.*, 1948, **16**, 128) this gives $D(\text{Ph}\cdot\text{CH}_2\text{–I}) = 43{\cdot}2 \pm 1{\cdot}8$ kcal./mole, which is in good agreement with Butler and Polanyi's value (43·7 kcal./mole) (*Trans. Faraday Soc.*, 1943, **39**, 19). The results of Blades, Blades, and Steacie (*Canad. J. Chem.*, 1954, **32**, 298) throw some doubt on the significance of the value quoted by Szwarc, but Schissler and Stevenson's electron-impact data (*J. Chem. Phys.*, 1954, **22**, 151) give a value for $D(\text{Ph}\cdot\text{CH}_2\text{–H})$ in good agreement with the value quoted by Szwarc.

The value $Q_{10} = 5{\cdot}2 \pm 1{\cdot}4$ kcal./mole may be used in conjunction with known bond-dissociation energies. For example, equation (10) can be transformed into

$$D(\text{Ph–I}) + D(\text{H–I}) \longrightarrow D(\text{Ph–H}) + D(\text{I–I});\ -Q_{10} = -5{\cdot}2 \pm 1{\cdot}4 \text{ kcal.}$$

Combining this with the accurately known values at 298° K for D(H–I) and D(I–I) quoted above, gives the bond substitution energy I for H in benzene :

$$D(\text{Ph–H}) - D(\text{Ph–I}) = 40{\cdot}5 \pm 1{\cdot}6 \text{ kcal./mole} \quad . \quad . \quad . \quad . \quad . \quad . \quad (12)$$

Stated in this form the result seems preferable for the reason mentioned above and particularly because of the uncertainty of the present value for D(Ph–H). However, if this result (12) is combined with one of the recently quoted values D(Ph–H) = 101·4 kcal. (Ladacki and Szwarc, *Proc. Roy. Soc.*, 1953, *A*, **219**, 341) we obtain D(Ph–I) = 60·9 ± 1·8 kcal./mole.

From the new results together with some well-known heats of formation (see, *e.g.*, Timmermans, *op. cit.*), important C–C bond-dissociation energies as well as interesting heats of formation have been calculated. These are summarised in Table 3.

Table 3.

R	$Q_f(\text{RI}_{gas})$ (kcal./mole)	$Q_f(\text{R}_{gas})$ (kcal./mole)	D(C–C) in R–R (kcal./mole)	D(R–I) (kcal./mole)
CH_3	− 1·86	−31·03	82·3	54·6
$Ph\cdot CH_2$	−18·77	−36·63	45·4	43·2
Ph	−33·78	−69·14	97·8	60·9

All the results in Table 3 depend on the D(C–H) values used in calculating D(C–I). The C–H bond-dissociation energies employed were :

$D(\text{CH}_3\text{–H})$ = 101 kcal./mole (Szwarc, *Chem. Reviews*, 1950, **47**, 157)

$D(\text{Ph–H})$ = 101·4 kcal./mole (Ladacki and Szwarc, *Proc. Roy. Soc.*, 1953, *A*, **219**, 341)

$D(\text{Ph}\cdot\text{CH}_2\text{–H})$ = 77·5 kcal./mole (Szwarc, *J. Chem. Phys.*, 1948, **16**, 128)

For $D(\text{Ph}\cdot\text{CH}_2\text{–H})$ Szwarc's result has been used but this is markedly different from that obtained by VanArtsdalen (89·5 kcal./mole); Schissler and Stevenson (*J. Chem. Phys.*, 1954, **22**, 151), however, recently reported the value $D(\text{Ph}\cdot\text{CH}_2\text{–H}) = 77 \pm 3$ kcal./mole from electron-impact studies, in agreement with Szwarc's figure. Values derived from Grignard calorimetry may be compared with a selection of similar data obtained recently (see Table 4).

The values in Table 4 are generally in good agreement with those of Table 3, especially those in the third and the fourth column. The high value for Q_f ($Ph{\cdot}CH_{2\,gas}$) reported by VanArtsdalen is dependent on the $D(Ph{\cdot}CH_2{-}H)$ value used. Since this is 12 kcal./mole

TABLE 4.

R	$Q_f(RI_{gas})$ (kcal./mole)	$Q_f(R_{gas})$ (kcal./mole)	D(C–C) in R–R (kcal./mole)	R–I bond length (Å)
CH_3	−2·8,[a] −4·3[b]	−32·1[d]	84·4[d]	2·13 (spec.),[f] 2·28 (E.D.)[f]
$Ph{\cdot}CH_2$	−26·4[c]	−37·4,[d] −49·4[e]	46·8[d]	
Ph	−38·35[b]	−69·7[b]	102·4[d]	2·02 (E.D.)[g]

[a] Carson, Hartley, and Skinner, *Proc. Roy. Soc.*, 1949, *A*, **195**, 500. [b] Carson, Carson, and Wilmshurst, *Nature*, 1952, **170**, 320. [c] Gellner and Skinner, *J.*, 1949, 1145. [d] Roberts and Skinner, *Trans. Faraday Soc.*, 1949, **45**, 339. [e] Anderson, Scheraga, and VanArtsdalen, *J. Chem. Phys.*, 1953, **21**, 1258. [f] Allen and Sutton, *Acta Cryst.*, 1950, **3**, 46. [g] Hugill, Coop, and Sutton, *Trans. Faraday Soc.*, 1938, **34**, 1529.

higher than Szwarc's value, the deviation from the other result quoted follows. Bond lengths are discussed below.

Bond-dissociation Energies.—The marked sequence

	$D(Ph{-}I)$	>	$D(CH_3{-}I)$	>	$D(Ph{\cdot}CH_2{-}I)$
Diff.	−6·3		−11·4		kcal./mole

is clear evidence for the non-additivity of bond dissociation energies. Evidence of this kind appears to have been first discussed by Baughan, Evans, and Polanyi (*Trans. Faraday Soc.*, 1941, **37**, 377).

The principal factors that increase the C–I disruption energy in iodobenzene, compared with that of CH_3–I, seem to be associated with increased interaction between the electrons of the iodine atom and those of the aromatic group. Previous published evidence for such increased interaction can be derived from the greater difficulty of hydrolysis for iodobenzene than for methyl iodide and from the formation of iodonium and iodoxy-compounds. Such evidence from reactivity differences might, however, refer to activated states of the molecule. The quantitative evidence obtained from evaluation of bond strengths refers to the molecules in the ground state and is substantiated by bond-length data. The decrease in the C–I bond length from methyl iodide to iodobenzene (Table 4) is indicative of increased electronic interaction. [Results from electron diffraction (2·02 and 2·28 Å) are more immediately comparable.] The calculated "double-bond character" of the phenyl–iodine linkage (~0·14) (Smyth, *J. Amer. Chem. Soc.*, 1941, **63**, 57) is of the same order as that derived from dipole-moment measurements. The value Ph–I = 1·4 D contrasted with CH_3–I = 1·6 D may be explained in terms of contributions from the annexed structures to the resonance hybrid of iodobenzene resulting in less negative iodine.

The decreased disruption energy of $Ph{\cdot}CH_2$–I compared with that of CH_3–I is probably mainly due to the large resonance energy of the benzyl radical compared with that of the methyl radical. A quantitative notion of the magnitude of the relative contributions from resonance energies of the radicals follows from arguments developed by Szwarc (*J. Chem.*

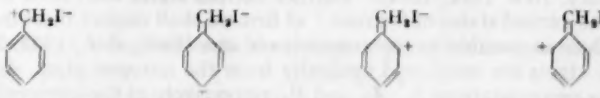
TABLE 5.

Compound	CH_4	PhMe	C_6H_6
D(R–H)	101	77·5	101
Exptl. resonance energies for R	0	23·5	0

Phys., 1950, **18**, 1660). Assuming the resonance energy of the methyl radical to be zero, he proposes that any difference between disruption energies $D(CH_3{-}H)$ and D(R–H) is to be attributed to the increased stabilisation of the radical R after disruption of the C–H bond.

On this basis the "experimental resonance energies" presented in Table 5 have been derived.

Neither bond length nor dipole moment data appear to be available for benzyl iodide. For benzyl chloride Parts (*Z. physikal. Chem.*, 1931, **12**, *B*, 323) points out that replacement of hydrogen in methyl chloride by phenyl increases the moment above that calculated by vectorial addition of the partial moments for the tetrahedral valency angle of 109° 29′ in the central carbon atom. This may be attributed to first-order conjugation, the origin of which is clearly seen by consideration of the influence of the annexed canonical forms



on the resonance hybrid of benzyl iodide. These considerations lead to prediction of a stronger bond in benzyl iodide than in methyl iodide, for which only the forms CH_3–I and CH_3^+–I^- are important. From the values for the bond-dissociation energies reported here, the magnitude of any such bond-strengthening appears to be small in comparison with the weakening of the bond due to radical-resonance stabilisation.

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*n–π Transitions in Azines.**

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The theory of *n*–π transitions in azines * is discussed and it is shown that simple molecular-orbital treatments, using the orbitals of the ground state, are not adequate to describe the upper state. A different approach is suggested and the characteristic properties of the *n*–π transitions are interpreted in terms of it.

It is now accepted that certain of the longer-wave-length absorption bands in pyridine, pyrazine, etc., are due to *n*–π transitions in which electrons are transferred from unshared pairs on the nitrogen atoms to π-orbitals of the rings (Platt, *J. Chem. Phys.*, 1951, **19**, 101). In this paper these transitions and the effects of substitution on them are discussed.

The n–π Transitions of Pyridine.—Since the wave functions of the states produced by *n*–π transitions in pyridine change sign on reflection in the plane of the molecule, they are automatically orthogonal to those of the ground state and of the excited states which are produced from it by π–π′ transitions. At first sight, the obvious model for calculations on such states is that of a system of seven electrons in the π-orbitals of a benzene-like ring, perturbed by the positive charge and unpaired electron on the nitrogen atom.

We have used two simple methods to attack this problem, a perturbation calculation and a conventional molecular-orbital treatment. We shall first consider each of these very briefly and show why they are inadequate.

According to simple molecular-orbital theory the two lowest states of the benzene negative ion are obtained by adding an electron to the unfilled orbitals of benzene. The most stable state will be of symmetry class E_{2u} and the other, which cannot be very much

* The term azine is used in its strictly systematic, generic meaning of an "aromatic" six-membered ring containing one or more nitrogen atoms.

less stable, of class B_{1g}. The orbitals for the added electrons in these states may be written:

$$\psi_I = 2\phi_1 - \phi_2 - \phi_3 + 2\phi_4 - \phi_5 - \phi_6$$
$$\psi_{II} = \phi_2 - \phi_3 + \phi_5 - \phi_6$$
$$\psi_{III} = \phi_1 - \phi_2 + \phi_3 - \phi_4 + \phi_5 - \phi_6$$

where ϕ_i is the $2p_\pi$ function on the i'th atom (Eyring, Walter, and Kimball, "Quantum Chemistry," Wiley, New York, 1944). Further excited states arise from the addition of an electron to the excited states of benzene: at first we shall neglect these in order to keep our model as close as possible to the conventional one (Reid, *ibid.*, 1953, **21**, 1906). In pyridine, if the atoms are numbered cyclically from the nitrogen atom, ψ_I, ψ_{II}, and ψ_{III} transform as the representations B_1, A_2, and B_1, respectively of the appropriate group C_{2v}.

The valence-state electron affinity of the nitrogen atom when six electrons have been spread evenly over the atoms of the ring corresponds quite closely to the process $sp^3V_4 \longrightarrow sp^4V_3$ and this is given as 12·24 ev. The corresponding value for the neutral carbon atoms is 0·69 ev (Mulliken, *ibid.*, 1934, **2**, 782).

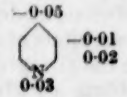
If we regard this difference of electronegativities as acting as a perturbation on the added electron we find that the first-order energy correction to any state is, apart from a constant, approximately equal to $c_1^2\delta$ where c_1 is the coefficient of the unshared electron on the nitrogen atom and $\delta \approx 11{\cdot}5$ ev. The perturbation therefore splits the E_{2u} state of the benzene ion, stabilising the state with wave function ψ_I by about 3·5 ev relative to that with wave function ψ_{II}. In second-order theory the wave functions ψ_I and ψ_{III} are mixed in such a way as to increase the charge on the nitrogen atom. If the energy separation between them is negligible compared with the perturbation, the resulting orbital has the form:

$$3\phi_1 - 2\phi_2 + \phi_4 - 2\phi_6$$

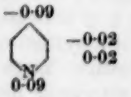
and the second-order perturbation energy is about 2 ev. In fact both the mixing and the perturbation energy would be somewhat smaller as the E_{2u}–B_{1g} separation is not quite negligible.

The treatment suggested above is the best that can be done as long as we restrict ourselves to theories in which we assign the extra electron to an orbital of the benzene ring, without allowing for the reorganisation of the other π-electrons. In view of the magnitude of the perturbation compared with the excitation energy of benzene it is clear this is not satisfactory and that other more highly excited states of the benzene ion should be included in our perturbation calculation. Instead of carrying through such a calculation we shall use conventional molecular-orbital theory, which is largely equivalent to it.

Since, as we shall show, this theory is also unsatisfactory we have not chosen the most plausible parameters. Instead we have considered two extreme cases. We have taken all the resonance integrals β equal, and the coulomb integral for nitrogen as equal to $\alpha + \delta\beta$. Since we are dealing with a seven-electron system in a framework of five unipositive carbon atoms and one dipositive nitrogen atom the value of $\delta\beta$ should be intermediate between the first and the second ionisation potential of nitrogen. We have considered two values of δ,



$\delta = 8$



$\delta = 4$

namely, $\delta = 8$ and $\delta = 4$. The first is probably too large and the second too small. The resulting roots and coefficients are shown in Tables 1 and 2. The coefficients for a system of an isolated nitrogen atom and a pentadienyl chain are included in Table 2 for comparison. The charge distributions derived from these calculations are shown in the annexed diagrams. The obvious fault of these calculations is their lack of self-consistency. The α-values assumed for nitrogen on the basis of electronegativity considerations lead to a final condition

of the nitrogen atom very different from that first assumed. The least that is required is a self-consistent method such as that suggested by Mann and Wheland (*ibid.*, 1949, **17**, 264). Such methods, however, are very laborious.

TABLE 1. *π-Electron energies for hypothetical perturbed benzene rings.*

	E_1	E_2	E_3	E_4	E_5	E_6
$\delta = 8$	−2·246	−1·686	−1·000	+0·163	+1·000	+1·769
$\delta = 4$	−4·473	−1·631	−1·000	+0·305	+1·000	+1·799

TABLE 2. *Coefficients for the orbitals of perturbed benzene rings.*

	$\delta = 8$				$\delta = 4$				$\delta = \infty$			
	c_1	c_2	c_3	c_4	c_1	c_2	c_3	c_4	c_1	c_2	c_3	c_4
E_1	0·985	0·121	0·013	0·004	0·945	0·223	0·056	0·025	1·000	0·000	0·000	0·000
E_2	0·086	−0·252	−0·504	−0·598	0·171	−0·203	−0·503	−0·617	0·000	0·287	0·500	0·573
E_3	0·000	0·500	0·500	0·000	0·000	0·500	0·500	0·000	0·000	0·500	0·500	0·000
E_4	+0·253	−0·568	−0·047	+0·576	+0·253	−0·545	−0·087	+0·571	0·000	0·573	0·000	0·573

Although not successful, these calculations suggest a more hopeful approach. Since, as shown in Table 2, the final state of the system is approximately described as a neutral nitrogen atom and pentadienyl radical in its ground state, we start our perturbation calculation from this extreme. We suppose that the upper state of the n–π transitions consists of a nitrogen atom in the rather unusual valence state $sp_xp_y\pi^2$ and a pentadienyl radical, and then allow the π-electron orbitals on the nitrogen atom to interact with those of the terminal atoms of the pentadienyl radical. The final charge distribution and energy are calculated in the usual way.

The appropriate ionisation potential I_N of nitrogen is about 12 ev. The electron affinity E_P corresponding to the lowest unfilled orbital of pentadienyl is not known. We shall assume a value of 1 ev, but even a large error in this estimate would not affect our qualitative conclusions.

The correct form of the lowest unfilled orbital of the pentadienyl radical is easily found to be $(\phi_2 - \phi_4 + \phi_6)/\sqrt{3}$, and so to a first approximation we may assign the last electrons to an orbital

$$\phi_1 + (\phi_2 - \phi_4 + \phi_6) \cdot \lambda/\sqrt{3}$$

where, if we neglect overlap,

$$\lambda = \frac{(1/\sqrt{3})\int\phi_1 H(\phi_2 - \phi_4 + \phi_6)\mathrm{d}\tau}{I_N - E_P}$$

$$= \frac{(2/\sqrt{3})\int\phi_1 H\phi_2\mathrm{d}\tau}{I_N - E_P}$$

$$= 2\beta'_{CN}/11\sqrt{3}$$

where β'_{CN} is roughly equal to the usual resonance integral β_{CN} of molecular-orbital theory. Unfortunately the absolute value of this quantity is uncertain, so that our further conclusions are largely qualitative. Assuming a reasonable value of 2 ev for β'_{CN}, we finally find $\lambda = 0{\cdot}21$, *i.e.*, that the charge transferred to the ring is about 0·05 of an electron.

The stabilisation energy

$$\Delta E = (2\beta_{CN}/\sqrt{3})^2/(I_N - E_P)$$

which is about 0·5 ev.

We do not attach any significance to these numerical values. They could be altered by as much as a factor of two by extreme assumptions about the parameters involved. The important conclusion is that delocalisation can cause a considerable stabilisation, without displacing the bulk of the seventh electron from the nitrogen atom.

We must now consider the nature of these states in more detail. There are two unpaired electrons, one in a hybrid σ-orbital on the nitrogen atom, directed away from the ring, and the other in a π-orbital partly on the nitrogen atom but mainly on the pentadienyl chain. The singlet–triplet separation between the two states which arise from this configuration will be roughly equal to $2K_{\sigma\pi}$, where $K_{\sigma\pi}$ is the exchange integral between these two electrons. In view of the uncertainty in λ we cannot estimate this exactly, but rough calculations show that it should be a good deal smaller than that in a π–π′ transition. The actual separation is not known with certainty (Reid, *loc. cit.*).

We conclude that, as has usually been assumed, the first singlet–singlet *n*–π transition of pyridine at just below 2600 Å is formally allowed. The rather low observed intensity of this transition in pyridine and in the diazines (Halverson and Hirt, *ibid.*, 1951, **19**, 711) can readily be understood. The occurrence of the *n*–π transition is associated with a complete reorganisation of the other π-electrons, so that the matrix element of the dipole moment is the product of two terms, one equal to $\int\phi_\sigma\mathscr{r}\phi_\pi d\tau$, where ϕ_σ and ϕ_π are the orbitals occupied by the electron which is directly involved, respectively, before and after the transition. The second factor, which is the overlap integral between the initial π-electron distribution and the final distribution of the six other π-electrons, is peculiar to this kind of transition and is responsible for the low intensity. We have evaluated this overlap factor as a sum of products of the overlap integrals between the benzene orbitals and the pentadienyl and the nitrogen orbitals. It is 0·49, thus leading to a decrease in intensity by a factor of four. If we further suppose that the transition is from an sp^2 nitrogen orbital to a π-orbital, then only the *s*-component of the nitrogen orbital makes any contribution to the intensity. We therefore expect a reduction of the intensity from that of a strongly allowed transition by a factor of twelve. This is probably sufficient to account for the low observed intensity.

The energy required to produce the *n*–π transition can be written $E = U_1 + U_2 - U_3$, where U_1 is the energy of excitation of the nitrogen atom from its $s^{1/3}p^{11/3}$ lower valence state to its sp^4 V_3 upper state, U_2 is loss of resonance energy during the transition, and U_3 is the gain in energy due to delocalisation, *i.e.*, the ΔE of the previous discussion. Using reasonable values for U_1 and U_2 we find a value of E of about 7 ev, instead of the observed 4 ev. We believe that the greater part of this discrepancy is due to the reorganisation of the σ-bonds in such a way as to make more use of the nitrogen *s*-orbital.

Substitution Effects.—It is recognised that the most important cause of the red shift of the 2600-Å band of benzene, which occurs on substitution, is the migration of charge into and out of the ring (Sklar, *ibid.*, 1942, **10**, 135). In general the shift gives a measure of the excess of this stabilisation in the upper state over that in the ground state. In the upper state of an *n*–π transition, as we have shown, there is already some negative charge on the carbon atoms. This inhibits further charge transfer from the substituents to the ring and so decreases the amount of stabilisation which can be effected in this way. It follows that substituents which can act as electron donors, but not as acceptors, should produce a blue shift of the *n*–π spectra, since they stabilise the ground state more than the upper state.

Halverson and Hirt's measurements (*loc. cit.*) confirm this prediction. In fact the blue shifts of the *n*–π bands in chloropyrazines mirror the red shifts in the π–π′ band at 2600 Å (cf. their Fig. 10). This suggests strongly that the ratio of the charge stabilisation effects in the upper and the lower states of the π–π′ transitions of the various chloropyrazines is roughly constant. Furthermore the data suggest a value of about 4·5 kcal. for the stabilisation due to charge migration in the ground state of chloropyrazine. On theoretical grounds that in chlorobenzene would be expected to be a little smaller.

Substituents which can act only as electron-acceptors should behave quite differently. They should produce larger stabilisations in the excited state than in the ground state and so should cause a red shift in the *n*–π bands. No spectra of suitable compounds seem to have been reported. The spectra of nitro- and cyano-pyrazines would be very useful in this respect.

The effect of substituents which can act both as donors in the ground state and acceptors in the excited state is not easily predicted. The methyl group, which falls into this class produces a small red shift in the α- and β-picolines and a rather larger blue shift (of 480 cm.$^{-1}$) in γ-picoline (Rush and Sponer, *J. Chem. Phys.*, 1952, **20**, 1847).

It must be noted that simple M.O. theory leads to identical results for the effects of substituents.

The Diazines.—The n–π transitions of polyazines can be treated by a generalisation of the theory developed for pyridine. We shall consider pyrazine.

There are clearly two n–π transitions in pyrazine corresponding to any one in pyridine. We shall deal with the lowest singlet–singlet transition. From simple symmetry considerations the wave functions for the upper states are of the form :

$$(1/\sqrt{2})(\chi_1 + \chi_2) \text{ and } (1/\sqrt{2})(\chi_1 - \chi_2)$$

where χ_1 and χ_2 correspond to hypothetical states obtained by exciting the first and the second nitrogen atom respectively. Transitions to $(1/\sqrt{2})(\chi_1 + \chi_2)$ are allowed and should have twice the intensity of the pyridine transition. Those to the state $(1/\sqrt{2})(\chi_1 - \chi_2)$ are forbidden.

The effect of the second nitrogen atom on the position of the n–π transition is twofold. Acting as an electronegative substituent it should produce a red shift in the 1 : 2- and 1 : 4-compounds. There will also be a much more complicated effect due to the splitting of degeneracy of the states $(1/\sqrt{2})(\chi_1 + \chi_2)$ and $(1/\sqrt{2})(\chi_1 - \chi_2)$ by the non-vanishing matrix-element $\int \chi_1 H \chi_2 d\tau$. There are good reasons for believing that this effect will be very small when the overlap of the unpaired σ-electrons is small. This is so in the 1 : 3- and 1 : 4-compounds but not in pyridazine. Experimentally there is a considerable red shift with respect to pyridine in the n–π band of pyrazine and pyridazine but not in that of pyrimidine (Halverson and Hirt, *loc. cit.*).

Discussion.—The treatment suggested above differs from that which is usually given, in rejecting the term diagram scheme. It is suggested that the great change in the nature of the π-bond skeleton accompanying an n–π transition completely changes the character of the π-orbitals, so that the orbital classification which is quite adequate for the description of π–π' transitions is no longer useful. If these conclusions are correct it follows that the intensities and positions of n–π transitions cannot be calculated from the same orbitals and level diagrams as are useful in the case of π–π' transitions.

The principal weakness of this approach is the neglect of σ-polarisation. We have assumed essentially that, in the upper state, the nitrogen atom achieves electrical neutrality at the expense of the π-electron system, without changing the σ-electron system. This cannot be quite correct, but we think that in view of the much greater polarisability of the π-electron system, it is a reasonable approximation.

We think it probable that the general method suggested in the previous section will be applicable to a variety of n–π transitions, *e.g.*, in conjugated ketones, nitroso-compounds, azobenzenes, etc. The feasibility of detailed semiempirical calculations along these lines is being investigated at Oxford.

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Organosilicon Compounds. Part XI. The Alkali-catalysed Cleavage of Substituted Benzyltrimethylsilanes.*

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The kinetics of the alkali-catalysed cleavage of substituted benzyltrimethylsilanes in aqueous methanol have been studied spectrophotometrically. The reaction is markedly facilitated by electron-withdrawing substituents in the benzyl group, and the effects of substituents agree well with their Hammett σ constants. The simplest mechanism consistent with the experimental facts is of the synchronous bimolecular (S_N2) type.

There are several examples in the literature of the breaking of Si–CH_2·C_6H_4X bonds by aqueous or aqueous-alcoholic alkali (*e.g.*, Kipping, *J.*, 1908, **93**, 457; Kipping and Steele, *J.*, 1928, 1431; Bygdén, *J. prakt. chem.*, 1917, **96**, 86; Benkeser and Brumfield, *J. Amer. Chem. Soc.*, 1951, **73**, 4770). The benzyl group itself is cleaved from silicon less readily than triphenylmethyl, 9-fluorenyl, and diphenylmethyl groups but markedly more readily than phenyl and alkyl groups (Hauser and Hance, *ibid.*, p. 5846; Gilman, Brook, and Miller, *ibid.*, 1953, **75**, 4531). We now report the first kinetic study of the alkaline cleavage of C–Si bonds, having examined spectrophotometrically the cleavage of seventeen benzyltrimethylsilanes, X–C_6H_4·CH_2·$SiMe_3$, by aqueous-methanolic alkali (*i.e.*, X·C_6H_4·CH_2·$SiMe_3$ + HOY $\xrightarrow{OY^-}$ X·C_6H_4·CH_3 + YO·$SiMe_3$, where Y = H or Me).

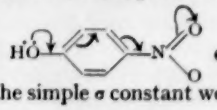
Kinetic Results.—The cleavages are of first order within a run since the concentration of alkali remains constant, and the rate-constant, k_1, at a fixed alkali concentration is independent of the initial concentration of silane. The reaction is also of first order in alkali, since the specific rate constant k_s ($= k_1/[MOH]$) is independent of the alkali concentration [MOH], as the following example shows. The figures refer to the cleavage of *p*-(trimethylsilylmethyl)benzanilide (initially 10^{-3}M) in 39 wt.-% aqueous methanol at 49·7°.

10^3 × [NaOH], (M)	971	728	486	243	121	60·7
10^4k_1 (min.$^{-1}$)	1970	1430	990	496	233	123
10^3k_s (min.$^{-1}$ mole^{-1} l.)	203	196	204	204	193	203

However, the cleavage of the anions Me_3Si·CH_2·C_6H_4·CO_2^- involves reaction between two negative ions, and the first-order specific rate constant rises markedly with increasing ionic strength, as shown by the following data for the *para*-isomer in 5 wt.-% water–methanol at 49·7°:

[NaOH] (M)	1·023	0·869	0·767	0·526	0·396	0·130
10^3k_s (min.$^{-1}$ mole^{-1} l.)	3·26	3·02	2·83	2·53	2·23	1·67

Table 1 shows the specific rate constants k_s for a particular alkali concentration, the Arrhenius activation energies E, and the log A factors, where $k_s = A\exp(-E/RT)$.

para- *and* meta-*Substituents.*—The order of ease of cleavage of the *m*- and *p*-X·C_6H_4·CH_2·$SiMe_3$ compounds may be seen from Table 1, and the reaction is very clearly facilitated by electron-withdrawal in X. The following table of deviations shows that when log k_s is plotted against the Hammett σ constants for the substituents (Jaffé, *Chem. Reviews*, 1953, **53**, 191) the points lie well about a straight line of slope 4·88 through the point for X = *p*-NO_2, provided that the σ^* constant is used for the *p*-NO_2 group. The σ^* constant (see Jaffé, *loc. cit.*) represents the effect of a substituent *para* to a phenolic or amino-group, when resonance interaction of the type  enables the substituent to withdraw electrons more effectively than the simple σ constant would require.

* Part X, *J.*, 1954, 4266.

Neglecting the *p*-MeO point, for which the rate constant used is only approximate (see p. 131), the standard deviation from the line of the σ value for the six substituents with well-established σ constants (H, *p*-Me, *p*-Cl, *p*-Br, *m*-Cl, *p*-NO_2) is only 0·014 (mean deviation, 0·009), and if all the points (except X = *p*-$CO{\cdot}NH_2$, see below) are included for which

TABLE 1. *Cleavage of* X·C_6H_4·CH_2·$SiMe_3$ *by alkali in* 39 *wt.-% water–methanol at* 49·7°.

X	λ (mμ)	[NaOH] (M) [a]	k_s [b]	*E* (cal.)	log *A* [c]
p-NO_2	315	$7{\cdot}4 \times 10^{-3}$	$52{\cdot}6$ [d]	13·7 [e]	8·84
o-NO_2	330	$7{\cdot}4 \times 10^{-3}$	$14{\cdot}1$ [d]	13·7 [e]	8·30
p-CO·NHPh	301	0·13	0·201	18·4 [f]	11·72
p-$CO{\cdot}NH_2$	256	0·13	0·183	—	—
o-CO·NHPh	305	0·98	$1{\cdot}53 \times 10^{-2}$	23·9 [f]	14·37
p-CO_2^-	255	0·97	$9{\cdot}40 \times 10^{-3}$	19·7 [f]	11·32
o-Cl	230	0·97	$2{\cdot}26 \times 10^{-3}$	—	—
m-Cl	230	0·97	$1{\cdot}83 \times 10^{-3}$	28·2 [d,g]	16·5 [d]
m-CO·NHPh	221	0·97	$9{\cdot}1 \times 10^{-4}$ [d]	—	—
p-Br	240	1·0	$5{\cdot}61 \times 10^{-4}$	—	—
p-Cl	230	0·97	$4{\cdot}03 \times 10^{-4}$	25·9 [g]	14·14
p-Me_3Si	235	1·0	$2{\cdot}80 \times 10^{-4}$	29·3 [g]	16·25
o-CO_2^-	285	0·97	$1{\cdot}39 \times 10^{-4}$	22·9 [h]	11·61
m-CO_2^-	292·5	0·98	$5{\cdot}95 \times 10^{-5}$	21·5 [h]	10·32
H	275	0·96	$2{\cdot}90 \times 10^{-5}$	29·5 [g,d]	15·43 [d]
p-Me	230	1·0	$5{\cdot}6 \times 10^{-6}$ [d]	—	—
p-MeO	234	1·0	$\sim 7 \times 10^{-7}$ [d]	—	—

[a] Approximate alkali concentration at which listed specific rate was measured. [b] Specific rate constant (k_1/[NaOH]) in $min.^{-1}$ $mole^{-1}$ l. [c] By extrapolation from measurements at 25° (k_s = 8·7 and 2·34 $min.^{-1}$ $mole^{-1}$ l. for the *p*- and the *o*-compound, respectively) and 35°. [d] Less accurate than other data. [e] From measurements at 25° and 35°. [f] From measurements at 50°, 40°, and 30°. [g] From measurements at 50° and 40°. [h] From measurements at 53°, 45°, and 40°. [i] Calc. on basis of time in minutes.

Jaffé lists σ or, where appropriate, σ^* values the standard deviation is still only 0·045. The high value of the Hammett ρ constant, given by the slope of the line, reflects the high sensitivity of the reaction to polar influences in the benzyl group.

TABLE 2. *Deviations from Hammett* log k_s–σ *plot* (ρ = 4·88).

X	*p*-NO_2	*p*-CO·NHPh	*p*-$CO{\cdot}NH_2$	*p*-CO_2^-	*m*-Cl	*m*-$CO{\cdot}NH_2Ph$	*p*-Br
− log k_s	−1·721	0·697	0·738	2·027	2·737	3·041	3·251
σ, calc.	1·270	0·786	0·766	0·50	0·357	0·294	0·250
σ (or σ^*)	1·270	—	(0·627)	—	0·373	0·280 [a]	0·232
σ (calc.) − σ	0·000	—	(+0·139)	—	−0·016	+0·014	+0·018

X	*p*-Cl	*p*-Me_3Si	*m*-CO_2^-	H	*p*-Me	*p*-MeO
− log k_s	3·395	3·553	4·225	4·538	5·252	6·155
σ, calc.	0·222	0·190	0·051	0·015	−0·159	−0·344
σ (or σ^*)	0·227	0·09 [b]	0·104	0·000	−0·170	−0·268
σ (calc.) − σ	−0·005	+0·10	−0·053	+0·015	+0·011	−0·076

[a] Is actually σ for *m*-$CO{\cdot}NH_2$. [b] σ^* value, from Benkeser and Brumfield (*J. Amer. Chem. Soc.*, 1953, **75**, 2421).

The deviation of the *p*-$CO{\cdot}NH_2$ point from the line is only apparent since the σ^* value for this group is derived from only one reaction and is subject to a standard deviation of 0·201. Our results indicate σ^* values for *p*-$CO{\cdot}NH_2$ and *p*-CO·NHPh of 0·766 and 0·786, respectively (the rates of cleavage are very close for these two substituents, with that for *p*-CO·NHPh slightly the greater, as expected in view of the electron-withdrawing effect of the phenyl group). The σ^* value used for the *m*-CO·NHPh group is actually that for *m*-$CO{\cdot}NH_2$; no doubt the σ^* value for *m*-CO·NHPh should be slightly greater than this, and our results indicate a value of +0·29.

There is no σ^* value for the *p*-CO_2^- group, and use of the σ value (+0·132) gives a point well away from the line. Undoubtedly this group requires a σ^* value, and our figures

indicate one of *ca.* 0·50, but this cannot be regarded as accurate because our data do not allow extrapolation of the rate constant to zero ionic strength, which is strictly required for reaction of this negatively charged entity. This uncertainty applies also to the *meta*-carboxylate-ion compound. (Other difficulties in applying the Hammett equation to charged substituents are discussed by Jaffé, *loc. cit.*)

Of particular interest is the ten-fold increase in rate, relative to that of benzyltrimethylsilane, caused by a *p*-Me_3Si substituent, which confirms that this group, in spite of its $+I$ effect, can effectively withdraw electrons from the ring by expansion of the valency shell of the silicon atom (d_π–p_π bonding). The *p*-Me_3Si group here withdraws electrons more strongly than its σ^* value of +0·09 would indicate (Benkeser and Brumfield, *loc. cit.*). Our results suggest a σ^* value of +0·19 for *p*-Me_3Si, and it may be that the group responds to the very strong demand for electron-withdrawal in the cleavage reaction.

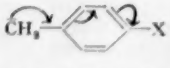
The activating influence of a *p*-NO_2 group is so great that *p*-nitrobenzyltrimethylsilane is cleaved readily by 39 wt.-% aqueous alcohol alone ($k_1 = 6{\cdot}43 \times 10^{-5}$ at 49·7°).

The Mechanism of the Cleavage.—The simplest mechanism consistent with experimental observations is one of a synchronous bimolecular (S_N2) type:

$$YO^- + R_3Si{\cdot}CH_2{\cdot}C_6H_4{\cdot}X \longrightarrow \underset{\text{(transition state)}}{\overset{\delta-}{YO}\cdots SiR_3\cdots\overset{\delta-}{CH_2}{\cdot}C_6H_4{\cdot}X} \longrightarrow YO{\cdot}SiR_3 + {}^-CH_2{\cdot}C_6H_4{\cdot}X$$

(followed by the rapid reaction $X{\cdot}C_6H_4{\cdot}CH_2^- + HOY \longrightarrow X{\cdot}C_6H_4{\cdot}CH_3 + OY^-$), where Y = H or Me. Electron-withdrawal in X aids reaction partly by facilitating the approach of the OY^- ion to silicon but mainly by increasing the ease of separation of the benzyl group with the electrons of the Si–C bond. We have seen that where a *para*-substituent has a σ^* as well as a σ value the former must be used to represent its effect in the cleavage, and we suggest that this is because the separating benzyl anion has a lone-pair of electrons conjugated with the *p*-substituent (just as have *p*-substituted phenols and amines), and will be stabilized by resonance interaction, such as, *e.g.*, (I). Any effect stabilizing the separating anion will also stabilize the transition state, and it is understandable that σ^* constants must be used to relate structure and reactivity.

Electron withdrawal by a substituent, whether by $-I$ or $-T$ effects or both, will stabilize the separating anion (II) and the greater is the lowering of the activation energy

(I) (II) 

by such stabilization the greater will be the amount of double-bond character of the CH_2–aryl bond in the transition state, and the more rigid will be the transition state and the lower its entropy, and hence the lower the A factor. Table 1 shows that, in general, increase in E is accompanied by increase in A. Plot of log A against E, in fact, gives points lying well about a straight line. [The greatest deviations are for X = *o*- and *m*-CO_2, when the log A factors are relatively low as expected for reaction between negative ions (Laidler, "Chemical Kinetics," McGraw-Hill Book Co., New York, 1950, pp. 132—135) but this effect is not present when X = *p*-CO_2^-, possibly because of the greater separation of the charges.] The Hammett equation can be applied to the cleavage reaction, not because of the constancy of the entropy terms, but because these terms are proportional to the enthalpy terms (cf. Brown and Hudson, *J.*, 1953, 883; Jaffé, *loc. cit.*).

We have found that benzyltriphenylsilane is more readily cleaved by aqueous-ethanolic alkali than is benzyltri-*p*-tolylsilane, so that electron-release in R hinders the cleavage of R_3Si–$CH_2{\cdot}C_6H_5$ compounds. This is consistent with the above mechanism if in the transition state the Si–OY bond is formed to a slightly greater extent than the Si–benzyl bond is broken, so that the silicon atom is slightly negatively charged in the transition state relative to the ground state. (This may not be true for, say, the *p*-nitrobenzyl compounds, in which bond-breaking may be more important than bond-making.) Benzyltriphenylsilane is more readily cleaved than benzyltrimethylsilane, in accord with the more

rapid alkaline hydrolysis of triphenylsilane than of trialkylsilanes, which also involves predominant nucleophilic attack on silicon (Price, *J. Amer. Chem. Soc.*, 1947, **69**, 2600; Gilman and Dunn, *ibid.*, 1951, **73**, 3404).

Reaction by the above mechanism should be sterically hindered by large R groups, and benzyl-*n*-propyl-di*iso*propylsilane, is much less reactive than benzyltrimethylsilane, though this may in part be due to the additional electron release to silicon.

The facts are equally consistent with a mechanism in which a quinquecovalent-silicon intermediate is rapidly formed and then decomposes in the rate-determining step :

$$YO^- + R_3Si{\cdot}CH_2{\cdot}C_6H_4{\cdot}X \overset{\text{Fast}}{\rightleftharpoons} YO{-}R_3\bar{S}i{-}CH_2{\cdot}C_6H_4{\cdot}X \xrightarrow{\text{Slow}} YO{\cdot}SiR_3 + {}^-CH_2{\cdot}C_6H_4{\cdot}X$$

The ground state must be taken as the trialkylbenzylsilane whether or not the intermediate has real existence, and relative to this ground state the effects of electron-withdrawal in X, of electron release in R, and of steric hindrance will be in the same direction in both mechanisms. Analogous intermediates have been proposed for the cleavage of Si–C bonds by alkali (Gilman, Brook, and Miller, *loc. cit.*) and by lithium amide (Hauser and Hance, *loc. cit.*), and also for the alkaline hydrolysis of triarylsilanes (Gilman, Dunn, and Hammond, *J. Amer. Chem. Soc.*, 1951, **73**, 4499) but in no case are there theoretical or experimental grounds for rejecting the synchronous bimolecular (S_N2) type of attack. In the neutral hydrolysis of organofluorosilanes the evidence that the silicon atom is more negative in the transition state than in the ground state, which Swain, Esteve, and Jones (*ibid.*, 1949, **71**, 965) interpret as proving the existence of intermediate $H_2\overset{+}{O}{-}R_3\bar{S}i{-}F$ is equally consistent with a modified S_N2 mechanism (Hughes, *Quart. Reviews*, 1951, **5**, 268; see also Sommer and Rockett, *J. Amer. Chem. Soc.*, 1951, **73**, 5130). Until there is evidence to the contrary it seems reasonable to accept the simple S_N2 mechanism for alkaline cleavage of Si–C and for other reactions involving nucleophilic attack on silicon. It is of interest that in nucleophilic reactions of Z_2POCl compounds (Z = alkyl or alkoxy) the balance of evidence is in favour of a synchronous S_N2 mechanism rather than an initial attachment of the nucleophilic reagent with expansion of the valency shell of the phosphorus atom (Dostrovsky and Halman, *J.*, 1953, 502, 505, 511, 516).

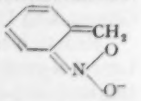
Effects of Change of Medium.—The following figures for the three cases studied show that in 39 wt.-% water–methanol the reaction is faster by roughly the same factor in each case than in 5 wt.-% water–methanol.

X in $Me_3Si{\cdot}CH_2{\cdot}C_6H_4X$	*p*-CO·NHPh		*o*-CO·NHPh		H	
Wt.-% of H_2O	39	5	39	5	39	5
$10 \times$ [NaOH] (M)	4·86	4·91	9·70	9·78	9·66	9·81
$10^4 \times k_1$ (min.$^{-1}$ mole^{-1} l.)	2040	1240	153	88·0	0·290	0·176
Ratio of specific rates	1·65 : 1		1·74 : 1		1·65 : 1	

Both mechanisms proposed above involve dispersal of charge in the transition state, and increasing polarity of the medium as the water content is increased should lower the reaction rate (Ingold, " Structure and Mechanism in Organic Chemistry," Bell and Sons, London, 1953, p. 347). However, addition of water also moves the equilibrium $MeO^- + H_2O \rightleftharpoons MeOH + OH^-$ towards the right, and we suggest that hydroxide ion is more nucleophilic towards silicon than methoxide ion, although the opposite order holds for attack on carbon (Bunnett and Davis, *J. Amer. Chem. Soc.*, 1954, **76**, 3011).

Increase in ionic strength would also be expected to lower the reaction rate (except for the reactions of the carboxylate ion compounds which will be discussed in a later paper). We have not, however, observed significant change in specific rate constant for cleavage of *p*-(trimethylsilylmethyl)benzanilide over a range of high alkali concentrations (see p. 126) or of trimethyl-*p*-nitrobenzylsilane over a range of much lower alkali concentrations (0·003—0·02M).

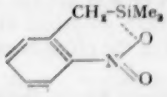
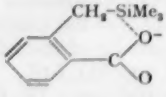
ortho-*Substituents.*—Since the reaction site is separated from the ring by a methylene group, *ortho*-substituents probably have inappreciable primary steric effects, but they

may have significant secondary steric effects by interference with mesomeric stabilization of the transition state. For example, steric interference will suppress contributions to the stability of the forming *o*-nitrobenzyl anion from structures such as 

which require coplanarity of the methylene and nitro-groups. Electrostatic repulsion between the forming negative charge and the nearby existing negative charge will undoubtedly raise the energy of the transition state in the case of the *o*-CO_2^- substituent.

However, the order of ease of cleavage of *o*-X·C_6H_4·CH_2·$SiMe_3$ compounds is (X =)NO_2>CO·NHPh>Cl>CO_2^->H, which is explicable in terms of polar effects alone. The NO_2 and CO·NHPh groups (relative rates for *p*- and *o*-compounds are 3·8 : 1 and 13 : 1 respectively) withdraw electrons by both $-I$ and $-T$ effects, and thus activate strongly from the *ortho*-position, but less so than from the *para*-position from which the $-T$ effect is most powerful (Ingold, *op. cit.*, pp. 267—269). The Cl substituent has a $-I$ and a weaker $+T$ effect, and since the former is most effective from the *ortho*-position this substituent activates more from here than from the *para*-position, and even than from the *meta*-position (relative rates of *p*-, *m*-, and *o*-compounds, 1 : 4·5 : 5·5). The CO_2^- group has a strong $+I$ effect opposed by a $-T$ effect, and the powerful operation of the $+I$ effect from the *ortho*-position markedly reduces activation by this group relative to its influence in the *para*-position (relative rates of *p*-, *m*-, and *o*-compounds, 69 : 0·4 : 1).

The small difference in reactivity between *o*- and *p*-nitrobenzyltrimethylsilane is not such that the "enhanced stability" of the *o*-compound requires any special explanation, such as the chelation (III) suggested by Benkeser and Brumfield (*J. Amer. Chem. Soc.*, 1951, **73**, 4770). However, the analogous chelation (IV) provides an alternative explanation for the relative stability of the *o*-(trimethylsilylmethyl)benzoate ion. The comparative weakness of the *o*-(trimethylsilylmethyl)benzoic acid [chelation (IV) would be

(III)   (IV)

acid-strengthening] and the absence of unusual features in the ultra-violet absorption of the *o*-(trimethylsilylmethyl)benzoate ion (Eaborn and Parker, *J.*, 1954, 939) are arguments against chelation existing to an extent which would have detectable kinetic consequences.

Experimental

M. p.s and b. p.s are corrected.

Preparation of Benzylsilane Derivatives.—Preparations of *o*-, *m*-, and *p*-X·C_6H_4·CH_2·$SiMe_3$ compounds in which X = Cl, CO_2H, and CO·NHPh have been described previously (Eaborn and Parker, *loc. cit.*).

Interaction of excess of benzylmagnesium chloride in ether and fluorotriphenylsilane, fluorotri-*p*-tolylsilane, and difluorodi*iso*propylsilane gave, respectively, benzyl-triphenylsilane (50%), m. p. (from EtOH) 99° (Found: C, 85·6; H, 6·5. Calc. for $C_{25}H_{22}Si$: C, 85·7; H, 6·5%), *-tri*-p-*tolylsilane* (70%), m. p. (from light petroleum) 105° (Found: C, 85·7; H, 7·2. $C_{28}H_{28}Si$ requires C, 85·6; H, 7·2%), and *-fluorodiisopropylsilane* (70%), b. p. 256°, n_D^{25} 1·4874 (Found: C, 70·3; H, 9·5%; equiv., 230. $C_{12}H_{21}FSi$ requires C, 69·6; H, 9·4%; equiv., 224).

Interaction of chlorotrimethylsilane in ether with the *p*-methylbenzylmagnesium bromide and *p*-methoxybenzylmagnesium chloride and with the lithium aryl from *p*-chlorobenzyltrimethylsilane gave, respectively, p-*methylbenzyltrimethylsilane* (45%), b. p. 211·5°, n_D^{25} 1·4917 (Found: C, 73·8; H, 10·0. $C_{11}H_{18}Si$ requires C, 74·1; H, 10·2%), p-*methoxybenzyltrimethylsilane* (10%), b. p. 142°/44 mm., 238°/760 mm., n_D^{25} 1·5002 (Found: C, 67·4; H, 9·2. $C_{11}H_{18}OSi$ requires C, 67·4; H, 9·3%), and *trimethyl*-p-*trimethylsilylbenzylsilane* (53%), b. p. 151·5°/45 mm., 250°/760 mm., n_D^{25} 1·4915 (Found: C, 66·1; H, 10·4. $C_{13}H_{24}Si_2$ requires C, 66·0; H, 10·2%).

Benzylfluorodi*iso*propylsilane and *n*-propyl-lithium in ether (initially at −20°, and then at the b. p. for 2 hr.) gave *benzyl*-n-*propyldiisopropylsilane* (80%), b. p. 187°/46 mm., 292°/760 mm., n_D^{25} 1·5050 (Found: C, 77·4; H, 11·4. $C_{16}H_{28}Si$ requires C, 77·4; H, 11·4%).

Nitration of Benzyltrimethylsilane.—Benzyltrimethylsilane (82 g.) was added during 45 min. to a well-stirred solution of fuming (95%) nitric acid (53 g.) in acetic anhydride (23 g.), kept below 10°. After being allowed to warm to room temperature during 24 hr. the mixture was added cautiously to a stirred slurry of ice and aqueous ammonia. Ether-extraction was followed by washing and drying (Na_2SO_4) of the ethereal extract and removal of the ether. The residue was fractionated in a column equivalent to *ca.* 30 plates, to give unchanged benzyltrimethylsilane (2 g.), trimethyl-*o*-nitrobenzylsilane (66·5 g., 65·3%), b. p. 124°/10 mm., n_D^{25} 1·5258, and the *p*-isomer (11·5 g., 11·2%), b. p. 146—147°/10 mm., n_D^{25} 1·5395. The physical constants agree with those given by Benkeser and Brumfield (*loc. cit.*).

Kinetic Measurements.—Methanol–water mixtures of s.g. (15·6°) 0·896 (39 wt.-% water) or 0·810 (5 wt.-% water) were used as solvents. Alkali solutions were carbonate-free.

Equal volumes of organosilane and alkali solutions (pre-warmed for fast runs) were mixed in a glass-stoppered vessel which was placed in a thermostat (constant to ±0·02°). Samples were withdrawn at intervals and diluted with the same solvent at room- or ice-temperature, and the optical density (at the wave-length, λ, given in Table 1) was measured with a Unicam S.P. 500 spectrophotometer. For reactions of half-life >60 hr. sealed tubes were used. Reactions were followed to >70% completion in most cases but for X = H, Me, and MeO the rate constants are based on the first 40, 20, and 5%, respectively, of reaction.

The rate-constant k_1 is given by:

$$k_1(t_2 - t_1) = 2{\cdot}303 \log (D_1 - D_\infty)/(D_2 - D_\infty)$$

where D_1, D_2, and D_∞ are the optical densities at times t_1, t_2, and infinity. For fast reactions D_∞ was obtained from reaction mixtures after more than ten times the half-life, but usually it was obtained by use of the appropriate solution of the substituted toluene, $X{\cdot}C_6H_4{\cdot}CH_3$. Values of k_1 were obtained from the slope of the straight-line plot of log $(D_t - D_\infty)$ against t.

The following typical run involved 39 wt.-% water–methanol at 49·7°:

X = *o*-CO·NHPh. [NaOH] = 0·971M.

Time (min.)	10	20	30	45	65	90	120	160	—
10^3D	609	564	526	475	429	378	343	313	279 *
10^5k_1 (min.$^{-1}$)	—	147	145	149	143	150	149	152	—

* Obtained from solution of *o*-toluanilide.

k_1 from graph, $1{\cdot}49 \times 10^{-3}$ min.$^{-1}$.

Reaction Products.—The identities of these were confirmed by isolation (in the case of solids) and by their ultra-violet absorption spectra. Hydrolysis of C–N bonds of anilides and amides seemed negligible under reaction conditions. The products were not investigated for X = Me or MeO.

Cleavage of Triarylbenzylsilanes.—A solution of benzyltriphenylsilane (2·5 g.) and potassium hydroxide (7·5 g.) in 95% aqueous ethanol (75 ml.) was boiled for 4 hr. and then added to water. Ether-extraction was followed by drying (Na_2SO_4) of the ethereal layer and removal of the ether. The solid left was dried in a vacuum-desiccator, and shown to contain 86% of triphenylsilanol by use of the Karl Fischer reagent (Gilman and Miller, *J. Amer. Chem. Soc.*, 1951, **73**, 2367). Benzyltri-*p*-tolylsilane similarly gave a solid containing 47% of tri-*p*-tolylsilanol.

A solution of benzyltriphenylsilane (5·0 g.) and potassium hydroxide (8·0 g.) in 95% ethanol (75 ml.) was boiled for 4 hr. and then added to water. The solid which separated was washed with water, and dried. It had m. p. and mixed m. p. of 154—156° and was almost pure triphenylsilanol (3·7 g., representing a minimum of 94% cleavage).

Cleavage of Trialkylbenzylsilanes.—A solution of trimethylbenzylsilane (16·4 g.) and potassium hydroxide (20 g.) in 95% aqueous ethanol (100 ml.) was boiled for 8 hr. and then added to water. Ether-extraction followed by drying (Na_2SO_4) and fractionation of the ethereal extract gave toluene (6·0 g., representing 65% of cleavage) and unchanged trimethylbenzylsilane (3·5 g., a 21% recovery).

Similar treatment of benzyl-*n*-propyldi*iso*propylsilane led to 94% recovery of unchanged material. No cleavage products were observed.

We thank Mr. H. R. Allcock who prepared *p*-bromobenzyltrimethylsilane and *p*-(trimethylsilylmethyl)benzamide and examined their cleavage reactions.

UNIVERSITY COLLEGE, LEICESTER. [*Received, September 18th*, 1954.]

Intramolecular Hydrogen Bonds and the Association and Solubilities of Substituted Benzoic Acids.

By Mansel Davies and D. M. L. Griffiths.

[Reprint Order No. 5755.]

The influence of intramolecular bonding upon the dimerisation and solubilities of some simple benzoic acid derivatives has been studied, and the results are discussed with particular reference to the energy changes associated with these processes. Infra-red data are presented for one case (*o*-methoxybenzoic acid) where they allowed a direct determination of the intramolecular bond energy.

The influence of what is now known as an intramolecular hydrogen bond upon the properties of *ortho*-substituted phenols and benzoic acid derivatives has long been known (Pfeiffer, *Annalen*, 1913, **398**, 137). The earlier studies such as those of von Auwers on molecular weights in solution, or of Sidgwick and Baker on volatility and solubility effects, have frequently been reviewed (see, *e.g.*, Hunter, *Ann. Reports*, 1946, **43**, 141). Infra-red, dipole-moment, and vapour-pressure studies (*inter al.*, Davies, *ibid.*, p. 6; Martin, *Nature*, 1950, **166**, 474; Lüttke and Mecke, *Z. physikal. Chem.*, 1950, *B*, **196**, 56; Wolf and Weghofer, *ibid.*, 1938, *B*, **39**, 194) have provided relevant information in some cases. Nevertheless, relatively few data are available on the energy of intramolecular hydrogen bonds. The present account describes the assessment of this factor in some substituted benzoic acids where its evaluation has been attempted from heats of solution, heats of association, and spectroscopic measurements.

Experimental

Infra-red Spectra.—The infra-red observations were made with a Grubb–Parsons S.3 spectrometer and a quartz prism. The absorption ascribed to the solute was that determined after allowing for the absorption by the solvent in the same cell at the same temperature. The type of cell and the experimental procedure have been described (Thomas, *J.*, 1951, 3307). To eliminate interference from the association band in carbon tetrachloride it was necessary to work at a concentration below 0·004M in a 10-mm. absorption cell. Concentrations were deduced from the peak optical densities.

Solubilities.—These were determined as described by us (*Trans. Faraday Soc.*, 1953, **49**, 1405), using Money and Davies's saturator design (*J.*, 1934, 400). Dried "AnalaR" potassium hydrogen phthalate was the ultimate standard.

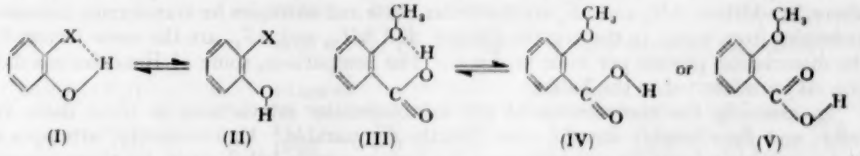
Distribution Studies.—These were made with the same temperature and analytical control as the solubilities. The frequency and period of shaking to ensure equilibrium was checked in each case, and adequate time was allowed for the complete separation of the layers: in some cases the latter period alone was more than an hour.

Materials.—"AnalaR" chemicals were used when procurable. The chloroform was freed from alcohol shortly before use, dried, and kept in the dark. The characteristics of some of the other materials after purification are given briefly (all m. p.s are the total corrected temperature ranges of melting): (*iso*-$C_5H_{11})_2O$, b. p. 172·5—173·8°/760 mm., free from peroxide; $Ph{\cdot}CO_2Et$, fractionated, b. p. 81·6°/7·6 mm., neutral; *o*-$C_6H_4(OMe){\cdot}CO_2H$, m. p. 101·5—102·0°, equiv. = 152·15 ± 0·25 (calc.: 152·14); *p*-$C_6H_4(OMe){\cdot}CO_2H$, m. p. 183—185°, equiv. = 152·15 ± 0·05; *p*-$C_6H_4(OH){\cdot}CO_2H$, m. p. 215·5—216·5°, equiv. = 137·8 ± 0·7 (titration indicator, bromothymol-blue; calc.: 138·12).

Results and Discussion

Infra-red Study.—The intramolecular equilibrium between *cis*- (or bonded, I) and *trans*- (or free, II) hydroxyl groups in *ortho*-substituted benzenes, whilst frequently observable in the O–H stretching mode absorptions, cannot in many cases be directly evaluated therefrom. Among the reasons for this are the unsatisfactory resolution of the component absorptions for (I) and (II), or the diffuse nature of the absorption of (I), or interference

from other absorptions, very frequently the association band arising from dimeric and higher aggregates of both (I) and (II). The uncertainties in this respect, even for the halogenophenols, have recently been emphasised (Lüttke, Mecke, and Rossmy, *J. Chem. Phys.*, 1953, **21**, 1606). However, we have found the conditions for *o*-methoxybenzoic acid in carbon tetrachloride to be favourable. Fox and Martin (*Nature*, 1939, **143**, 199) located the O–H absorption for (III) at 3362 cm.$^{-1}$, for (IV) (and/or V) at 3530 cm.$^{-1}$, whilst the association band is centred near 2950 cm.$^{-1}$. The intensities of the individual absorptions due to (III) and (IV) can thus be separately measured. To evaluate the equilibrium constant K = [Monomeric III]/[Monomeric IV], the relation from Beer's law, [A] = $[1/(\alpha_A d)] \ln (I_0/I)$ was applied to the absorption maxima, where α_A is the molar extinction coefficient of A. In fact, K was not determined but a factor proportional to it, *i.e.*, $\bar{K} = K \cdot \alpha_{IV}/\alpha_{III}$. Individual values of $\bar{K}$ at 23° ± 1° were 8·6, 10·0, 8·8, 9·0, 10·1, *i.e.*, 9·3 ± 0·6; similarly at 48° ± 2°, $\bar{K}$ = 6·3 ± 0·4; at 72° ± 2°, $\bar{K}$ = 4·2 ± 0·3. On the assumption that the ratio α_{IV}/α_{III} does not vary with temperature,* these figures give for the equilibrium (III) ⇌ (IV), ΔH = 3·3 kcal./mole with a *maximum* uncertainty of 0·5 kcal./mole.



(I) (II) (III) (IV) (V)

As the equilibrium constants are determined from direct observations of both components and the ΔH value is deduced with the minimum of assumptions, it may be accepted as a standard for comparison with other less direct estimates.

Association Studies.—It is well known that the association of hydroxylic compounds is markedly reduced when the hydroxyl group is involved in intramolecular interactions (Hunter, *loc. cit.*). By the comparison of suitable cases it should be possible to estimate the energy involved in this internal process or, at least, to determine the extent to which the association energy is changed. The hydroxy- and methoxy-benzoic acids have been examined in this respect—the former in a number of solvents.

First, an accurate determination of the dimerisation equilibrium constant, K^S_{12} = [Monomer]^2/[Dimer] in the solvent S is required. This may be obtained over a range of temperatures by the distribution of the acid between water and an immiscible solvent (Moelwyn-Hughes, *J.*, 1940, 850). The principal assumptions involved are that the acid forms an ideal monomeric solute in water (correction for slight ionisation is readily made), and that both monomer and dimer are ideal solutes in the immiscible solvent. In these conditions it follows (Gross and Schwarz, *Monatsh.*, 1930, **55**, 287; Moelwyn-Hughes, *loc. cit.*) that :

$$C_S/C_W = K_D = K_{D1} + 2(K^S_{D1}/K^S_{12})C_W$$

Here C_S is the observed total molar concentration in the non-aqueous solvent, C_W the un-ionised acid concentration in water, *i.e.*, $C_W = C_W^t(1-\beta)$, where C_W^t is the total aqueous acid molarity and β the degree of ionisation. K_{D1} is the distribution constant for the monomer, *i.e.*, [Monomer in S]/[Monomer in H_2O]. Conformity to the above assumptions leads to a linear plot of K_D against C_W from which K_{D1} and K^S_{12} can be evaluated. Significant deviations from this simple behaviour (usually for $C_W > 1$M) can readily be recognised (Davies and Griffiths, *Z. physikal. Chem.*, in the press). They have been avoided in what follows by considering the data only for those concentration regions, of adequate extent, where the above relation holds. It should be noted that the dimerisation constants (K^S_{12})

* Theory does not suggest that α itself would be temperature-dependent. The most immediately relevant evidence in favour of its constancy is the quantitative agreement of the infra-red values of equilibrium constants and heats of association for a variety of solutes with those determined by osmotic methods (cf., *inter al.*, Mecke, *Discuss. Faraday Soc.*, 1950, **9**, 161, and some half-dozen, as yet unpublished, further examples studied in these Laboratories).

are those for the solvent S saturated with water. Whilst there is an increasing number of examples of the type discussed here in which saturation with water has been proved to have little effect on K^{S}_{12} (Davies and Griffiths, *loc. cit.*; unpublished vapour-pressure lowering, spectroscopic, and distribution data in these Laboratories), what is of immediate interest in the present study is the difference between K^{S}_{12} and, more particularly, ΔH^{S}_{12} values in the wet solvent for different benzoic acid derivatives. However, for benzoic acid in benzene we would specifically indicate that the value of K^{S}_{12} from freezing points in the dry solvent at 5·5° (Barton and Kraus, *J. Amer. Chem. Soc.*, 1951, **73**, 4561) is identical with that evaluated from distribution studies at 6° for the wet solvent, *i.e.*, $6{\cdot}4 \times 10^{-4}$ mole/l. (Wall, *ibid.*, 1942, **64**, 472). The corresponding ΔH^{S}_{12} values are: for the dry solvent, 8·4 ± 0·4 kcal./mole (Wall and Baines, *ibid.*, 1945, **67**, 898); and for wet benzene, 8·7 kcal./mole (Hendrixson, *Z. anorg. Chem.*, 1897, **13**, 73).

From the distribution data the following values of $10^4 \times K^{S}_{12}$ (mole/l.) are found in benzene at 40°: benzoic acid, 32; *p*-methoxybenzoic acid, 47; salicylic acid, 950; *o*-methoxybenzoic acid, 4360. These results measure the great reduction of association in the *ortho*-compounds. The newly determined equilibrium constants are given in Table 1 where, in addition, ΔH_1 and ΔS_1 are the molar heats and entropies for transferring monomer molecules from water to the organic solvent, and ΔH_{12} and ΔS_{12} are the same factors for the dissociation process per mole of dimer. For comparison, some of Hendrixson's data (*loc. cit.*) are inserted in the Table.

In assessing the contribution of the intramolecular interactions in these data, the *ortho*- and *para*-isomers are the most strictly comparable. Unfortunately, attempts to find a suitable solvent for comparison of the hydroxy-acids failed, since, for those solvents in which the solubility of the *p*-hydroxy-acid was adequate (*e.g.*, di*iso*pentyl ether), the association was too small to be measured.

It might be expected that the partial molar heat contents of the *ortho*- and *para*-isomers would be more nearly equal in aqueous than in organic solutions, as the water will *tend* to break down any intramolecular hydrogen-bonding. This effect is seen in the sign and magnitude of the difference (~1 kcal./mole) in the ΔH_1 values for *p*- and *o*-methoxybenzoic acids. The fact that this difference is not equivalent to the intramolecular bond energy could be most readily explained by assuming that the interaction is only partly suspended for the *ortho*-isomer in water (cf. salicylic acid, p. 137).

A much more certain measure of the intramolecular bonding is provided by the difference in the values of ΔH_{12} for the *ortho*- and the *para*-isomers. If we try the reasonable assumption that in forming the dimer the intramolecular interaction within *o*-methoxybenzoic acid is completely eliminated, the difference in the association energies between *para*- and *ortho*-isomers, *i.e.*, (10·0 − 3·4) kcal./mole of dimer, gives the energy of two intramolecular bonds. This value, 3·3 kcal./mole per bond for wet benzene, agrees well with the direct spectroscopic determination in dry carbon tetrachloride.

A comparison of the ΔH_{12} values for salicylic and benzoic acid in benzene would, in the same way, give 1·4 kcal./mole as the energy of the *ortho*-effect in the former, but the very uncertain status of this value is shown by the almost identical ΔH_{12} values for these acids in chloroform. Apart from the fact that salicylic acid should more properly be compared with its *para*-isomer, there is little doubt that the inconsistency here arises largely from the persistence of some interaction of the phenolic hydroxyl with the adjacent carboxylic group even when the latter is involved in dimerisation. In the methoxy-compound this could not occur, as the only active hydrogen there is (apparently) completely inactivated within the dimer. The existence of a residual *ortho*-interaction in salicylic acid dimer is shown by the absence from its solutions of any absorption near that of a "free" hydroxyl group (Martin, *Nature*, 1950, **166**, 474). The energy of this residual interaction varies from benzene to chloroform solutions.

The influence of the solvent upon the association is well illustrated by the values of $10^4 K_{12}$ for benzoic acid at 35°; in benzene 27; chloroform 210; di*iso*pentyl ether 6200; ethyl benzoate 28,600. The ΔH_{12} values, for both benzoic and salicylic acid, show the same influence, and the variation in these cases is not determined by the dielectric properties (cf. Moelwyn-Hughes *et al.*, *J.*, 1951, 1249). In the oxygenated solvents specific

interactions with the acid solutes are involved (Flett, *J. Soc. Dyers Col.*, 1952, **68**, 59) and for salicylic acid the varying intramolecular bonding complicates the relations.

Solubilities.—Our determinations of the solubilities of benzoic and salicylic acids in carbon tetrachloride were made at a number of temperatures from 25° to 55°. At 25° the

TABLE 1. *Distribution data.*

Solute	Solvent *	Temp. (c)	K_{D1}	10^4K_{12} (mole/l.)	ΔH_1 (kcal./mole)	ΔS_1 (cal./mole °K)	ΔH_{12} (kcal./mole)	ΔS_{12} (cal./mole °K)
$C_6H_5{\cdot}CO_2H$	B	—	—	—	Wall and Baines's data		8·4 ±0·4	15·4 ±1·0
	C	15·00°	3·5$_6$ ±0·1	83±3	1·03 ±0·15	6·1 ±0·7	8·2 ±0·2	18·8 ±0·7
		44·95	4·2$_1$ ±0·1	320±2				
	A	25·00	8·9$_1$ ±0·06	6000 ±140	−2·6 ±0·3	—	0·8 ±0·3	—
		40·00	7·40 ±0·04	6200 ±120				
		55·00	5·96 ±0·04	6700 ±120				
	D	35·05	31·4 ±0·2	28,600 ±500	Only very slight association			
o-$C_6H_4(OH){\cdot}CO_2H$ ...	B	10 and 40	—	—	Hendrixson's data		5·6	—
	C	10	2·3	340	Hendrixson's data		7·7	—
		40	2·6	950	0·6	5·8	7·8$_5$	20·6
		15·05	4·21 ±0·06	387	±0·1	±0·5	±0·2	±0·7
		35·03	4·50 ±0·05	938				
	E	40·00	0·498 ±0·005	47·7 ±0·9	2·0$_5$ ±0·1	5·2 ±0·3	12·2 ±0·4	28·$_5$ ±1·2
		55·00	0·584 ±0·005	110 ±2				
		70·00	0·671 ±0·005	263 ±4				
	D	35·05	79·3 ±0·8	—	—	No detectable association		
p-$C_6H_4(OH){\cdot}CO_2H$ ...	A	25·00	0·409 ±0·003	—	−4·8$_5$ ±0·1	No detectable association		
		55·00	0·194 ±0·001	—				
	D	15·07	5·62 ±0·05	4260 ±300	—	Only very slight association		
o-$C_6H_4(OMe){\cdot}CO_2H$ ...	B	40·08	4·40 ±0·05	4360 ±100	−0·45 ±0·1	1·5± ±0·3	3·4$_0$ ±0·2	9·3 ±0·8
		50·00	4·31 ±0·05	4990 ±250				
		60·00	4·23 ±0·05	5770 ±260				
		70·08	4·14 ±0·05	7400 ±400				
p-$C_6H_4(OMe){\cdot}CO_2H$ ...	B	40·08	2·90 ±0·05	46·7 ±1·2	0·50 ±0·1	3·7 ±0·3	10·0 ±0·2	21·2 ±0·9
		50·00	2·97 ±0·05	75·5 ±1·5				
		60·00	3·04 ±0·05	117 ±3				
		70·08	3·10 ±0·05	190 ±4				

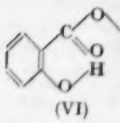
* A = (*iso*-$C_5H_{11})_2O$; B = C_6H_6; C = $CHCl_3$; D = $Ph{\cdot}CO_2Et$; E = CCl_4

values were: for benzoic acid 0·3422 molal (0·0500 mole-fraction unit); and for salicylic acid 0·01910 molal (0·002930 mole-fraction unit). Within the experimental accuracy the temperature variation strictly conformed to $\ln N_S = \Delta S/\boldsymbol{R} - \Delta H/\boldsymbol{R}T$, where N_S is the mole-fraction of solute in the saturated solution and ΔS and ΔH are the molar entropy and enthalpy changes on solution. Accordingly, we have not quoted further individual solubility values but give in Table 2 the ΔS and ΔH values with estimates of the maximum

uncertainty in them. For benzene and water good data were already available both for these acids and for the *meta*- and *para*-isomers. These have now been evaluated in the same way: for the aqueous solutions N_S is the mole-fraction of un-ionised solute at saturation. For all the aqueous solutions the apparent heats of solution are markedly temperature-dependent (cf. Davies and Griffiths, *Trans. Faraday Soc.*, 1953, **49**, 1405).

These solubility parameters include variations due to differing extents of association and/or solvation in the saturated solutions, but apart from these variations, the differences between them arise principally from changing interactions in the solid state. It appears that in benzene the heats of solution can be accounted for in simple terms. For the *m*- and *p*-hydroxy-compounds they are 4·0 and 3·3 kcal./mole greater than for benzoic acid. This is clearly an expression of the interaction of the phenolic hydroxyl groups in these cases, *e.g.*, the *p*-hydroxy-acid will be packed in the solid in an array AϕB·BϕA·AϕB·BϕA·, etc., where A is the carboxyl and B the hydroxyl group. Mecke (*Z. Elektrochem.*, 1944, **50**, 57) has determined this hydroxyl–hydroxyl interaction energy (in benzene solutions) as 3·5 kcal./mole for phenol and 4·4 kcal./mole for benzyl alcohol.

The heat of solution of salicylic acid in benzene is intermediate between those of benzoic and the *p*-hydroxy-acid. This is qualitatively what would have been expected: the fact that it is not coincident with that of benzoic acid indicates that in such a structure as (VI) the *o*-hydroxy-group, although possibly " bound " in the geometrical sense, can still contribute appreciably to the intermolecular field holding the molecules together in the solid lattice (cf. preceding section). On this basis it would follow that the residual intermolecular contribution of the *o*-hydroxy-group is of the order of (8·6—6·9) = 1·7 kcal./mole in the solid state. Comparison of the values of ΔH(solution) for benzoic and salicylic acid in carbon tetrachloride gives a difference, identical within the possible errors, of 1·4 kcal./mole. Confirmation of this interpretation is provided by the fact that the heat



(VI)

TABLE 2. *Molar heats and entropies of solution.*

Solute	Solvent	Temp., °C	ΔH, kcal./mole	ΔS, cal./mole °K	Ref.*
$C_6H_5{\cdot}CO_2H$	C_6H_6	25—80	6·9 ± 0·1	18·0 ± 0·3	*a*
	CCl_4	25—55	8·05 ± 0·15	21·0 ± 0·5	*b*
	H_2O	5·0	$4{\cdot}5_4$	—	*c*
		22·5	$6{\cdot}2_6$	—	,,
		45·0	$7{\cdot}7_3$	—	,,
		65·0	$9{\cdot}0_5$	—	,,
o-$C_6H_4(OH){\cdot}CO_2H$	C_6H_6	20—65	$8{\cdot}6_3$ ± 0·15	18·1 ± 0·15	*c*, *d*, *e*
	CCl_4	25—55	$9{\cdot}4_8$ ± 0·25	20·2 ± 0·8	*b*
	H_2O	5·0	$5{\cdot}9_8$	—	*c*
		22·5	$7{\cdot}2_0$	—	,,
		45·0	$7{\cdot}8_3$	—	,,
m-$C_6H_4(OH){\cdot}CO_2H$	C_6H_6	45—65	10·9	16·4	*e*
	H_2O	5·0	$7{\cdot}7_7$	—	*c*
		22·5	$7{\cdot}3_8$	—	,,
		45·0	$7{\cdot}4_0$	—	,,
		65·0	$9{\cdot}6_2$	—	,,
p-$C_6H_4(OH){\cdot}CO_2H$	C_6H_6	10—80	10·2 ± 0·15	13·3 ± 2·0	*e*
	H_2O	5·0	$7{\cdot}4_3$	—	*c*
		22·5	$8{\cdot}6_7$	—	,,
		35·0	$9{\cdot}4_3$	—	,,
		55·0	$13{\cdot}5_0$	—	,,

* (*a*) Chipman, *J. Amer. Chem. Soc.*, 1924, **46**, 2445. (*b*) Present work. (*c*) Seidell, " Solubilities of Organic Compounds," 3rd edn., Van Nostrand Co., New York, 1940. (*d*) Sidgwick and Ewbank, *J.*, 1921, **119**, 979; Desai and Patel, *J. Indian Chem. Soc.*, 1935, **12**, 131. (*e*) Walker and Wood, *J.*, 1898, **73**, 620.

of sublimation of salicylic acid is 1·0 kcal./mole greater that that of benzoic acid (Davies and Jones, *Trans. Faraday Soc.*, 1954, **50**, 1042).

The markedly varying heats of solution for these acids in water is probably due to the large and temperature-dependent rôle of solvation in that medium. Thus *p*-hydroxybenzoic acid forms a definite hydrate (Sidgwick and Ewbank, *loc. cit.*). The approximate equality and smaller temperature-dependence of the aqueous heats of solution for the *o*-

and *m*-hydroxy-acids suggest that hydration may be less important (or more temperature-independent) in these cases.

The solvent water, even if it does not succeed completely, will certainly tend to break down the intramolecular bonding in salicylic acid. The solubility data, however, give no clear evidence of this.

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The Absorption Spectra of Some Complex Ions of Analytical Importance.

By R. J. P. WILLIAMS.

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Some characteristic features of the absorption spectra of complex ions are discussed. The bands due to the ligand are modified by the polarising power of the cations and by the part played by the cation in the conjugation of the ligand. The spectra of certain ferrous complexes are due to allowed transitions in which an electron is excited into an orbital which interacts with the ligand; a partial electron transfer from the cation occurs. Some other cation complexes have similar spectra. The absorption spectra of certain ferric complexes are, it is suggested, due to 3*d*–3*d* transitions coupled with partial charge transfer to the cation. The intensity and the wavelengths of the absorption of many complexes can be satisfactorily understood on this basis.

IN recent years colorimetric methods have been increasingly used for the determination of metal ions in solution. Many of these methods have employed organic reagents which form coloured complexes, ML, with a limited number of cations. Often the absorption spectra of these complexes have been carefully measured but there has been little examination of the electron transitions responsible for the absorption. The following discussion will advance theoretical ideas to account for regularities now apparent in these spectra.

The absorption of light by the complexes ML can arise through transitions of (*a*) non-bonding electrons of the ligand, L, (*b*) non-bonding electrons of the cation, M, or (*c*) bonding electrons between M and L.

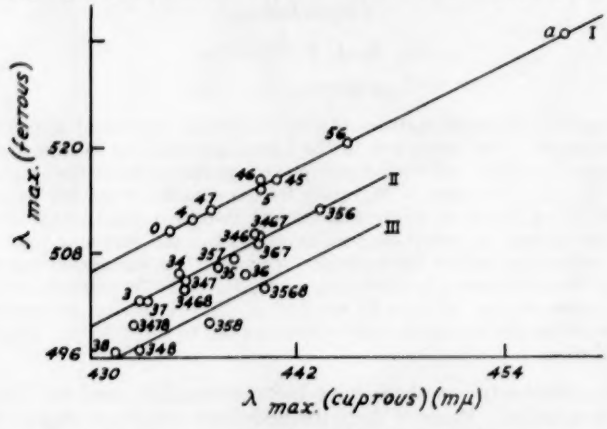
Transitions of Non-bonding Electrons of the Ligand.—In ionic complexes there are virtually no bonding electrons and the absorption of the complexes must be the sum of the absorption of M and L separately, but slightly modified by mutual polarisation. The polarisation of the ligand might well be expected to vary inversely with the radii of the cations, provided that the latter have constant charge. An example has been studied by Schwarzenbach, Anderegg, and Sallman (*Helv. Chim. Acta*, 1952, **35**, 1794) who measured the absorption spectra of the complexes, ML^-, formed by the ligand 2 : 5 : 1-$HO{\cdot}C_6H_3(NO_2){\cdot}CH_2{\cdot}N(CH_2{\cdot}CO_2H)_2$ with zinc, magnesium, calcium, and barium ions.

The spectra are similar to that of the ligand, L^{3-}, and to that of the proton complex, HL^{2-}, but both $\lambda_{max.}$ and $\epsilon_{max.}$ *fall* slightly with increasing stability of the complexes. The stabilities do not increase with the inverse of the radii, however, but are closely related to the ionisation potentials of the cations, $Zn^{II} > Mg^{II} > Ca^{II} > Ba^{II}$. Apparently the polarisation of the ligand is proportional to the electron affinity of the cation. Anderegg, Flascka, Sallman, and Schwarzenbach (*ibid.*, 1954, **37**, 113) measured the absorption spectra of the complexes of the same series of cations with a second ligand, related to (I), and again found that $\lambda_{max.}$ and $\epsilon_{max.}$ *fall* parallel with increasing stability

of the complexes. In the complexes of these ligands the cation reduces the possibility of quinonoid resonance, as does the proton, and the chelate ring in which it is bound cannot be conjugated with the aromatic ligands.

The relation between the stability of complexes and the positions of the ligand absorption band has also been measured in the series listed in Table 1. In three series, in one of which there is the same chelating bridge –N·C·C·O– as in (I), the value of $\lambda_{max.}$ *increases* with increasing stability of the complex in the order $Cu^{II} > Ni^{II} > Co^{II} > Zn^{II}$ (Irving and Williams, *J.*, 1953, 3192). The chelate ring in which the cation is bound is conjugated with the ligand in these cases but, despite the difference in its direction, the shift of the absorption band again follows the electron affinity of the cation. The effect

FIG. 1. *Comparative plot of $\lambda_{max.}$ of some cuprous– and ferrous–phenanthroline complexes. The numbers refer to positions of substitution of methyl groups in phenanthroline. (Note the point a for the 4 : 7-diphenyl compound)* (I) *Values in the absence of 3(8)-methyl groups.* (II) *Values for compounds with one 3(8)-methyl group.* (III) *Values for compounds with two 3 : 8-methyl groups.*



of a cation is not always so simply related to ionisation potentials, for in the absorption spectra of the porphyrin (Table 1) and phthalocyanine complexes (Anderson, Bradbrook, Cook, and Linstead, *J.*, 1938, 1151) the positions of the ligand absorption bands are shifted in the order $Ni^{II} > Co^{II} > Cu^{II} > Zn^{II}$. The complexes of these ligands are covalent, unlike those described above, and 3*d* orbitals are used in the bonding of cobaltous

TABLE 1. *Position of the ligand bands in some complexes* ($\lambda_{max.}$ *in* mμ).

	Cation						
Ligand	Cu^{II}	Ni^{II}	Co^{II}	Zn^{II}	Mn^{II}	H^{I}	Ref.
8-Hydroxyquinoline	412	400(430) *	406	373	396	355	(1)
Acetylacetone	296	294	282	280	—	273	(1)
2-*p*-Dimethylaminophenylazopyridine	570	550	540	538	540	470	(2)
Dipyridyl	298	308—296	305—295	—	280	280	(3)
o-Phenanthroline	—	307	304	270	—	265	(4)
Mesoporphyrin IX dimethyl ester	560	550	—	570	—	570	(5)
	525	515	—	535	—	530	(5)

(1) Sone, *J. Amer. Chem. Soc.*, 1953, **75**, 5207; see also Fernando, Emery, and Phillips, *ibid.*, p. 1983. (2) Klotz and Loh Ming, *ibid.*, p. 4159. (3) Yamasaki, *Bull. Chem. Soc. Japan*, 1937, **12**, 390. (4) Roberts and Field, *J. Amer. Chem. Soc.*, 1950, **72**, 4232. (5) Stern and Dezelic, *Z. phys. Chem.*, 1937, **180**, *A*, 131.

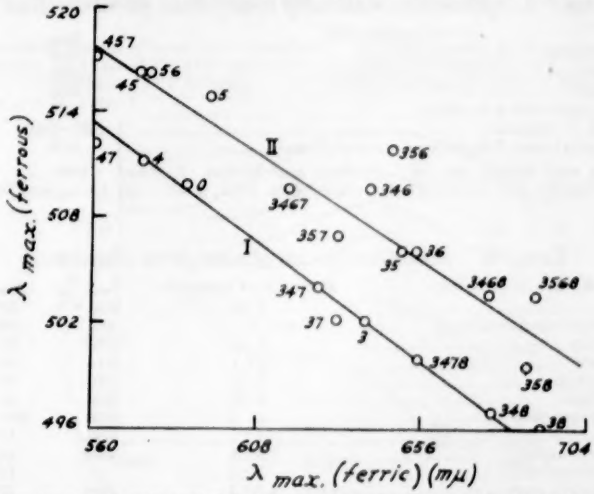
* The anomalous second peak in the nickel–oxine spectrum is discussed on p. **143**.

and nickel ions. In all the examples so far studied only small shifts in $\lambda_{max.}$ of the ligand absorption are brought about by complex formation.

Absorption due primarily to the Cation.—In the spectra of ferric, cuprous, and diamagnetic ferrous complexes with aromatic di-imines, such as *o*-phenanthroline and dipyridyl,

there are intense bands in the visible region which can be readily distinguished from the ligand bands around 270 mμ (Table 1). The bands in the visible region are not present in other similar cation complexes of the same ligands, *e.g.*, of nickel, cobaltous, or zinc ions (Roberts and Field, *loc. cit.*; Yamasaki, *loc. cit.*) and must be due therefore to electron transitions of the specific cations. The absorption spectra of these ferrous and cuprous complexes are very similar. Their extinction coefficients are invariably around 10^4, implying allowed electron transitions, and there is a linear 1 : 1 relation between $\lambda_{max.}(Fe^{II})$ and $\lambda_{max.}(Cu^{I})$ in the methyl-substituted phenanthroline complexes (Fig. 1; data from Brandt and Smith, *Analyt. Chem.*, 1949, **21**, 1313; McCurdy and Smith, *Analyst*, 1952, **77**, 846). Such a relation indicates that the electron transitions involved

FIG. 2. *A comparative plot of $\lambda_{max.}$ of some ferric– and ferrous–methylphenanthroline complexes. (The numbers refer to the positions of the methyl substituents in the phenanthroline molecule.) (I) Values in the absence of 5-methyl groups. (II) Values for compounds containing one 5(6)-methyl group.*



(Values for compounds containing two 5 : 6-methyl groups lie above line II.)

in the complexes are also similar. Intense absorption bands in the visible region are not found in other series of cuprous or ferrous complexes, *e.g.*, with chloride or cyanide, even if the latter are diamagnetic (Fromherz and Menschick, *Z. phys. Chem.*, 1929, *B*, **3**, 1; Samuel, Zamen, and Zubairy, *Indian J. Physics*, 1936, **9**, 491). The appearance of the bands requires both a conjugating and chelating di-imine and that the ferrous ion should be in the diamagnetic state with an electron configuration in which the 3*d* levels are filled, as in the cuprous ion, with either atomic or bonding electrons. An electron transition which accords with these features is the excitation of a 3*d* electron into a higher quantum level, such as the 5*p*, which can be coupled with the empty π levels of the ligand. The excitation suggested is a partial electron transfer *to the ligand*, which explains the shift to longer $\lambda_{max.}$ as the acceptor character of the ligand increases (Table 2). In other transition series the ruthenous and osmous cation complexes of phenanthroline and dipyridyl have similar absorption spectra (Brandt and Smith, *loc. cit.*; Burstall, Dwyer, and Gyarfas, *J.*, 1950, 953) and the electron transition involved is presumably similar too.

A comparison between the absorption spectra of the ferrous and ferric complexes of methylphenanthrolines (Fig. 2; Brandt and Smith, *loc. cit.*) shows that the sensitivity of the values of $\lambda_{max.}(Fe^{III})$ to changes in the substituents is greater than that of $\lambda_{max.}(Fe^{II})$ and that the shifts in $\lambda_{max.}$ are in opposite directions. The intensity of the ferric spectra is one-tenth of that of the ferrous. This low intensity suggests that the electron transition

is not an allowed one. A large number of other ferric complexes has been examined (Table 3). The position of maximum absorption in these complexes is also sensitive to substituents in the ligand. Examples amongst phenanthroline (Brandt and Gullstrom, *J. Amer. Chem. Soc.*, **1952**, **74**, 3532), 8-hydroxyquinoline (Molland, *Tidsskr. Kjemi*, 1941, **3**, 50), fatty acid (Kiss, Abraham, and Hegedius, *Z. anorg. Chem.*, **1940**, **244**, 98), and phenol (Brode and Wesp, *J. Amer. Chem. Soc.*, **1934**, **56**, 1037) complexes show that increase in the electron-donor properties, by such groups as methyl as opposed to nitro- or carboxyl, shifts the absorption to longer wave-lengths. The intensity ranges from that typical of forbidden transitions $\varepsilon_{max.} \ll 10^2$, to that of allowed transitions $\varepsilon_{max.} \simeq 10^4$ (Table 3 and Fig. 3). The weak absorption found in some of these ferric complexes arises from a 3*d*–3*d* transition (Bowen, *Quart. Reviews*, 1950, **4**, 243). This has been put beyond reasonable doubt in the case of ferric thiosulphate (Page, *Trans. Faraday Soc.*, 1953,

TABLE 2. *Absorption maxima of some ferrous phenanthrolines.*

o-Phenanthroline	$\lambda_{max.}$	Ref.
Unsubstituted	510	(1)
4 : 7-Diphenyl-	533	(1)
4-Hydroxy-	544	(2)
3-Ethoxycarbonyl-4-hydroxy-	561	(2)
Several 4 : 7-diamino-	530—560	(3)
8-Ethoxycarbonyl-7-hydroxy-4-methyl-2-aza-	605	(4)

(1) McCurdy and Smith, *loc. cit.* (2) Hale and Mellon, *J. Amer. Chem. Soc.*, 1950, **72**, 3217. (3) Wilkins, McCurdy, and Smith, *Analyt. Chim. Acta*, 1953, **8**, 46. (4) Irving and Williams, *Analyst*, 1952, **77**, 813.

TABLE 3. *Absorption spectra of some ferric complexes.*

Ligand (salt or complex)	Formula of complex	$\lambda_{max.}$	$\varepsilon_{max.}$	Ref.
Citrate	1 : 1	450 *	10^3 *	(1)
Acetate (maximum co-ordination)	—	465	50	(2)
m-Nitrophenoxide	1 : 1	510	50	(3)
p-Nitrophenoxide	1 : 1	515	30	(3)
Resorcinol complex	1 : 1	550	50	(3)
Ethyl acetoacetate	1 : 1	500	50	(3) (4)
Salicylaldehyde complex	1 : 1	530	800	(3) (4)
Salicylate	1 : 1	530	10^2	(3)
Phenanthroline complex	3 : 1	590	10^3	(5)
Acetylacetone complex	3 : 1	—	$10^{3\cdot5}$	(6)
8-Hydroxyquinoline complex	3 : 1	600	$10^{3\cdot7}$	(6)
Thiocyanate	3 : 1 (?)	525	$10^{4\cdot0}$	(7)
Thioglycollate	?	530	$10^{4\cdot0}$	(8)
3-Sulphosalicylate	1 : 1	510	$10^{3\cdot3}$	(9)
,,	2 : 1	460	$10^{3\cdot6}$	(9)
,,	3 : 1	425	$10^{3\cdot5}$	(9)

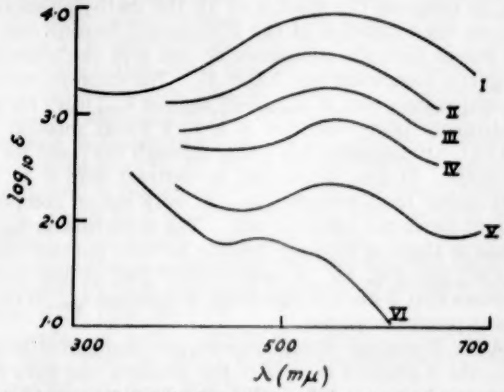
* There is no maximum in the spectrum as recorded, and the band at about these wave-lengths appears to have merged with the general absorption at shorter wave-lengths (1). This is also apparent in the formate and trichloroacetate complexes (Kiss, Abraham, and Hegedius, *loc. cit.*).

(1) Lanford and Quinan, *J. Amer. Chem. Soc.*, **1948**, **70**, 2900. (2) Reiss, Hazel, and McNabb, *Analyt. Chem.*, 1952, **24**, 1646. (3) Broumand and Smith, *J. Amer. Chem. Soc.*, 1952, **74**, 1013. (4) Herbst, Close, Mazzacua, and Dwyer, *ibid.*, p. 269. (5) Brandt and Smith, *loc. cit.* (6) Sone, *loc. cit.*; Henecka, *Ber.*, 1948, **81**, 179. (7) Ovenston and Parker, *Analyt. Chim. Acta*, 1949, **3**, 277. (8) Swank and Mellon, *Analyt. Chem.*, 1938, **10**, 7. (9) Agren, *Acta Chem. Scand.*, 1954, **8**, 266.

49, 635), and the similarity between the absorption of this complex and many other ferric complexes (Fig. 3) allows the argument to be extended to them. The usual 3*d*–3*d* transition, as found in the complexes of chromic and diamagnetic cobaltic, changes slightly in wave-length on the change of the ligand but the shifts are accompanied by little change in intensity (contrast Table 3; Kiss and Czegledy, *Z. anorg. Chem.*, 1938, **235**, 407; Linhard and Weigel, *Z. anorg. Chem.*, 1952, **271**, 101). The maximum absorption in these complexes has an extinction, $\varepsilon_{max.}$, of about 10^2. Now the cobaltic and chromic ions in their normal states have two unoccupied 3*d* levels which are used in the formation of covalent, inner-orbital, complexes and there is no possibility of increase in covalency by electron rearrangement. In the majority of ferric complexes

the ferric ion has five **3*d*** electrons all unpaired, so that these complexes are " ionic," outer-orbital complexes, with no **3*d*** binding. The increase of $\lambda_{max.}$ of the ferric complexes with increasing electron donation from the ligand indicates that the electron-acceptor properties of the ferric ion are increased in the excited state. This can come about if the transition involved, which is now assumed to be forbidden **3*d*–3*d***, is such as to vacate a **3*d*** level, making it available for bonding. Such a transition would be associated with a change in permanent dipole in the cation–ligand bond and could be considered as a partial electron transfer ***from the ligand*** to the cation, ***i.e.***, in the opposite direction from that which adequately explained features of the spectra of ferrous complexes. It is now more apparent why changes in substituents in phenanthroline produced opposed shifts in the absorption spectra of the ferric and ferrous complexes of this ligand (Fig. 2). The intensity of the spectra of the ferric complexes is thus linked with the size of the change in the permanent dipole on excitation. In the extreme case the transition could go over to a full electron transfer to the ferric ion, and an intensity of 10^4 would be expected

FIG. 3. *The absorption spectra of some ferric complexes. (I) Thiocyanate,* **3 : 1** *complex. (II) Catechol-* **3 : 5***-disulphonate,* **3 : 1** *complex. (III)* **3***-Sulphosalicylate,* **1 : 1** *complex. (IV) Salicylaldehyde,* **1 : 1** *complex. (V) Thiosulphate,* **1 : 1** *complex. (VI) Acetate, maximum complex formation. References are in the text and in Table* **3**.



(*Note :* Due allowance has been made for the formation of different complexes, and the extinctions given all refer to a single complex. Similarly data for other complexes can be obtained by reference to Table 3.)

as for an allowed transition. This case, it is suggested, is realised in ferric thiocyanate and in a number of other complexes in which ferric is co-ordinated through sulphur atoms, *e.g.*, thioglycollate (Swank and Mellon, *loc. cit.*). The suggestion that the spectra of the latter complexes are true charge-transfer spectra is strengthened by the relative instability of the complexes to light and by the fact that the absorption moves to longer wave-lengths as the number of ligands bound to the cation is increased (Rabinowitch, *Rev. Mod. Physics*, **1942**, **14**, 112). On the other hand, many ferric complexes have absorption of much lower intensity and are stable to light, and increase in co-ordination to them shifts the absorption maxima to shorter wave-lengths (Agren, *loc. cit.*; Harvey and Manning, *J. Amer. Chem. Soc.*, 1950, **72**, 4488; Swank and Mellon, *Analyt. Chem.*, 1937, **9**, 406). The shift to shorter wave-lengths with increasing co-ordination may well be due to increasing symmetry altering the splitting of the **3*d*** energy levels in the ferric ion, in accord with the idea that this weaker absorption is due to a **3*d*–3*d*** transition.

The argument furthermore predicts that bands of varying intensity from 10 to 10^4 should be found in certain other transition-metal ion complexes. The following absorption spectra appear of particular interest, since alternative explanations are lacking for their characteristics: the ruthenium(III) and osmium(III) complexes of sulphur-containing ligands (Ayres and Wells, *Analyt. Chem.*, 1950, **22**, 317) which differ from the other

Group VIII metal complexes excepting only ferric; the osmium(III) complex of dipyridyl (Dwyer and Gyarfas, *J. Amer. Chem. Soc.*, 1951, **73**, 2322); the octahedral complexes of manganese(III) with three molecules of oxalate or pentanedione (Cartledge, *ibid.*, 1952, **74**, 6015).

Details of the Spectra of Complexes of Di-imines.—A methyl substituent in an aromatic base such as phenanthroline or pyridine increases the basicity of the nitrogen (Herrington, *Discuss. Faraday Soc.*, 1950, **9**, 26; Irving, Cabell, and Mellor, *J.*, 1953, 3417; Brandt and Gullstrom, *loc. cit.*). Bjerrum (*Chem. Reviews*, 1950, **46**, 381) has shown that in a series of complexes of a given metal and a number of ligands derived by substitution from one parent compound the stability of the complexes is closely related to ligand basicity. The complexes of methylphenanthrolines would all be expected to be more stable than that of the parent compound, and the generalisation has been confirmed in some cases (Brandt and Gullstrom, *loc. cit.*; Irving, Cabell, and Mellor, *loc. cit.*) and is borne out by the values of oxidation–reduction potentials (Brandt and Smith, *loc. cit.*). It might have been expected therefore that all methyl groups would have shifted the absorption spectra of the phenanthroline complex of a given cation in the same direction. The following discussion of the absorption spectra of the ferrous and cuprous complexes will indicate why this expectation is not fulfilled.

It is not possible to compare the spectra of all the methylphenanthroline complexes of these two cations, as the formation of the 2(9)-methyl ferrous complexes is sterically hindered to such an extent that the complexes do not give the absorption characteristic of the ferrous diamagnetic complexes (see Table 4). The cuprous complexes are normal, however. Fig. 1, a comparative plot of $\lambda_{max.}(Fe^{II})$ against $\lambda_{max.}(Cu^{I})$ for methyl-substituted complexes, 2(9)-substituents being omitted, is a 1 : 1 linear relation in the absence of 3(8)-methyl groups, the continuation of line going through the point for the 4 : 7-diphenylphenanthroline complexes. It also shows that in contrast with 4- or 5-methyl groups a 3-substituent reduces rather than increases $\lambda_{max.}$ in both cation complexes, and that two such groups have about twice the effect of one. The reduction in $\lambda_{max.}$ is greater in the ferrous complexes than in those of cuprous, leading to three parallel relationships between $\lambda_{max.}(Fe^{II})$ and $\lambda_{max.}(Cu^{I})$ (see Fig. 1). A comparative plot of the extinction coefficients of these complexes shows that 3-methyl substituents decrease $\varepsilon_{max.}$ in the ferrous complexes but increase it in the cuprous complexes.

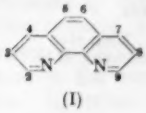
Unlike the 4- and the 5-position which are strongly conjugated to the nitrogen atoms in phenanthroline (I), the 3-position is *meta* to the nitrogen but *para* to the bond joining the two nitrogen-containing rings. A 3-methyl group will shorten this bond by increasing its double-bond character, whilst a 4- or a 5-methyl group will mostly alter the donor properties of the nitrogen. The shortening of the distance between the nitrogen atoms would be expected to have a greater effect on the ferrous spectra as the bonding orbitals here are d^2sp^3, which are very sensitive to bond-angle changes, whereas in the cuprous complexes the bonding is through the less sensitive sp^3 orbitals. Assuming then that it is the difference in directive power that largely affects the shifts in $\lambda_{max.}$, a 2-methyl group should behave, in the absence of steric hindrance, *e.g.*, in cuprous complexes, in the same way as a 4-methyl substituent. The values obtained by McCurdy and Smith (*loc. cit.*) confirm this: both $\lambda_{max.}$ and $\varepsilon_{max.}$ are increased, *e.g.*,

	$\lambda_{max.}$	$\varepsilon_{max.}$
Cuprous *o*-phenanthroline	435	7040
Cuprous 2 : 9-dimethyl-*o*-phenanthroline	455	7890

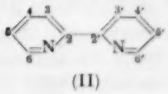
An examination of the absorption spectra of the cuprous and ferrous complexes of other aromatic bases again demonstrates the importance of the different directive influences of differently substituted methyl groups. In complexes with dipyridyl (II) (Cagle and Smith, *J. Amer. Chem. Soc.*, 1947, **69**, 1860; Hoste, *Analyt. Chem.*, 1950, **4**, 23), the values of $\lambda_{max.}$ and $\varepsilon_{max.}$ are as follows ($\varepsilon_{max.}$ in parentheses):

Ferrous		Cuprous	
Unsubstituted	522 (8650)	Unsubstituted	435 (4550)
3 : 3′-Dimethyl	526 (1770)	6 : 6′-Dimethyl	455 (6570)
4 : 4′-Dimethyl	529 (8470)		
5 : 5′-Dimethyl	510 (8310)		

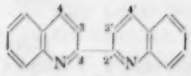
The 4 : 4′- and 6 : 6′-methyl groups, of which the 6 : 6′-groups have the expected greater effect on $\lambda_{max.}$ (the ferrous and cuprous complexes being assumed to behave similarly), increase $\lambda_{max.}$ and are *ortho* and *para* respectively to the nitrogen atoms of dipyridyl. The 5 : 5-methyl groups, *para* to the 2 : 2′-bond, decrease $\lambda_{max.}$, also much as expected, but the 3 : 3′-methyl groups, which would have been expected to induce a similar effect to that of the 5 : 5-groups, in fact increase $\lambda_{max.}$. The anomaly arises through the steric hindrance between these two 3 : 3′-methyl groups preventing the two pyridyl rings from



(I)



(II)



(III)

lying in the same plane, and hence instead of decreasing the length of the 2 : 2′-bond, these groups increase it. For the same steric reasons the value of $\varepsilon_{max.}$ is very low in these compounds. That such steric hindrance is present in the dipyridyls can be demonstrated by analogy with the effect of methyl substituents in diphenyl (O'Shaughnessy and Rodebush, *J. Amer. Chem. Soc.*, 1940, **62**, 2906), for it has been shown that 3 : 3′- but not 4 : 4′- or 5 : 5′-methyl groups eliminate the absorption band of diphenyl which is characteristic of the interaction between the two rings. This work also proves that the shift observed in the 5 : 5′-dimethyldipyridyl ferrous complex is intimately concerned with the co-ordination to the cation, for it is in the opposite direction to the shift produced by methyl groups in the same positions in diphenyl. In 3-methyldiphenyl (Braude, Sondheimer, and Forbes, *Nature*, 1954, **117**, 173) steric hindrance is very slight. Hoste (*loc. cit.*), and Irving and Williams (*Analyst*, *loc. cit.*), quote examples of the formation of cuprous and ferrous complexes of dipyridyl derivatives in which single 3-substituents do not prevent the formation of complexes with high extinction coefficients. In diquinolyl complexes of cuprous, where 4 : 4′-substituents [see (III)] behave as in dipyridyl and phenanthroline, a single 3-substituent does not lower the extinction coefficient very greatly, and it is noteworthy that $\lambda_{max.}$ decreases as expected from the presumed shortening of the 2 : 2′-bond produced by such groups in the absence of steric hindrance (Smith and Wilkins, *Analyt. Chim. Acta*, 1954, **10**, 139).

The absorption spectra of some terpyridyl ferrous complexes have been studied (Wilkins and Smith, *ibid.*, 1953, **9**, 338). 4-Methyl and 4-phenyl substituents have the expected effects, increasing both $\lambda_{max.}$ and $\varepsilon_{max.}$.

Spectra of Some Further Ferrous Complexes.—The classification of the intense spectra of the above diamagnetic complexes of ferrous as allowed transitions from the filled 3*d* shell (see p. 139) suggests that the similar, though much less intense, absorption of a large number of other ferrous complexes might well arise from the same transition, especially as the ligands with which ferrous shows such spectra are all conjugating and chelating imines (Table 4). It is clear from the Table, too, that as the number of these ligands which are co-ordinated to the cation is increased, the intensity of the absorption increases rapidly until it is equal to that of the diamagnetic complexes on six-fold co-ordination. Very similar rapid changes in absorption concomitant with change in paramagnetic moment of ferrous complexes have been frequently observed on further co-ordination of ferroporphyrins (Williams, *Biol. Review*, 1953, **28**, 381), but there is no absorption in the ferrous complexes of glycine, ethylenediamine, or *o*-aminobenzoic acid. Furthermore, it is known that ferrous complexes are abnormally stabilised when co-ordinated directly to an aromatic ring with ligands such as 8-hydroxyquinoline (Irving and Williams, *loc. cit.*; Albert and Hampton, *loc. cit.*). It appears probable that the absorption is due to the presence of a small proportion of the diamagnetic form of the ferrous complexes, the intensity of absorption around 400—600 mμ increasing as this proportion increases (see Table 4).

Nickel and Cobaltous Complexes.—Nickel perchlorate, when dissolved in water, has two weak absorption bands at $\lambda_{max.}$ 400 and 600 mμ and of $\varepsilon_{max.}$ 10—100. In many nickel complexes the absorption around 400 mμ is greatly increased without a corresponding

effect near 600 mμ (Kiss and Szabo, *Z. anorg. Chem.*, 1943, **252**, 172). In some of the paramagnetic complexes, *e.g.*, those of oxine, the extinction at these wave-lengths which cannot be attributed to the ligand (see Table 1) is of the order 10^3—10^4. Such extinction is too great to be attributed to a simple 3*d*–3*d* transition (McKenzie, Mellor, Mills, and Short, *J. Proc. Roy. Soc. N.S.W.*, 1944, **78**, 70; Sone, *loc. cit.*). Elsewhere (Williams, *J. Phys. Chem.*, 1954, **58**, 121) it has been pointed out that nickel complexes, such as that

TABLE 4. *Absorption spectra of some ferrous complexes.*

Ligand	$\lambda_{max.}$	$\epsilon_{max.}$	Magnetic moment, B.M.	Ref.
Picolinic acid, 2 : 1 complex	440	3×10^3	5·2	(1) (2)
,, plus cyanide	440	10^4	—	(1)
Pyrazine-2 : 3-dicarboxylic acid	495	3×10^3	—	(3)
Pyridine-2 : 5-dicarboxylic acid	415	2×10^3	—	(4)
Quinaldinic acid, 2 : 1 complex	515	3×10^3	5·2	(1) (2)
,, plus cyanide	515	10^4	—	(1)
5 : 6-Diphenylquinaldinic acid, 2 : 1 complex	515	4×10^3	—	(1)
,, ,, plus cyanide	515	10^4	—	(1)
Quinoxaline-2 : 3-dicarboxylic acid	520	3×10^3	—	(3)
Dipyridyl, 1 : 1 complex	435	2×10^3	5·2	(5) (6)
o-Phenanthroline, 1 : 1 complex	400—450	2×10^3	5·2	(7) (6)
2-Methylphenanthroline, 2 : 1 complex	440	10^3	5·2 (?)	(8) (6)
2-Chlorophenanthroline, 2 : 1 complex (?)	510	Weak	—	(8)
Dipyridyl, 3 : 1 complex	523	10^4	0·0	(9)
o-Phenanthroline, 3 : 1 complex	510	10^4	0·0	(9)
*cyclo*Hexanedione dioxime, 2 : 1 complex	464	3×10^3	—	(10)
,, ,, plus pyridine	531	10^4	—	(11)
,, ,, plus ammonia	541	10^4	—	(11)
Diacetyl dianil, 2 : 1 complex	600	Weak	—	(12)
Diacetyl di-*N*-methylimine, 3 : 1 complex	510	10^4	—	(12)

N.B. Many derivatives of 8-hydroxyquinoline also give red-yellow ferrous complexes (Albert and Hampton, *J.*, 1954, 505).

(1) Majumbar and Sen, *Analyt. Chim. Acta*, 1953, **8**, 369; 1953, **9**, 529; *J. Indian Chem. Soc.*, 1950, **27**, 245. (2) Cambi and Cagnasso, *Gazzetta*, 1953, **83**, 767. (3) Ley, Schwarte, and Munnish, *Ber.*, 1924, **57**, 349. (4) Chang and Reddick, *Analyt. Chem.*, 1954, **26**, 536. (5) Krumholtz, *J. Amer. Chem. Soc.*, 1949, **71**, 3654. (6) Basolo and Dwyer, *ibid.*, 1954, **76**, 1454. (7) Kolthoff, Leussing, and Lee, *ibid.*, 1950, **72**, 2173. (8) Irving, Cabell, and Mellor, *loc. cit.* (9) Brandt and Smith, *loc. cit.* (10) Banks and Byrd, *Analyt. Chim. Acta*, 1954, **10**, 129. (11) Griffing and Mellon, *Analyt. Chem.*, 1947, **19**, 1017. (12) Krumholtz, *J. Amer. Chem. Soc.*, 1953, **75**, 2163; see also Walter and Freiser, *Analyt. Chem.*, 1954, **26**, 217, for further examples of the absorption spectra of ferrous di-imine complexes.

with oxine, are adversely affected in stability if the ligand forces the cation out of either a planar or an octahedral arrangement despite the fact that the complexes are paramagnetic. Furthermore, the rates of exchange of nickelous ions from many paramagnetic complexes are low as compared with the corresponding exchange rates for cupric, cobaltous, and zinc ions (West, *J.*, 1954, 395). Low rate of exchange of an ion has been frequently correlated with covalent, and in the case of nickel, diamagnetic, forms of complexes (Taube, *Chem. Review*, 1952, **50**, 69). An absorption band, differing only in intensity from that at 400 mμ described above, is also found in diamagnetic nickel complexes. It has a maximum extinction coefficient greater than 10^4, implying that it must arise from an allowed transition. These lines of evidence suggest that there is a contribution to the properties of the (mostly) paramagnetic nickel complexes from their diamagnetic forms.

As ready excitation of a 3*d* electron from a full 3*d* shell seemed to be common to three series of cation complexes, *viz.*, ferrous, cuprous, and nickelous, it was sought in others. Most cobaltous complexes show weak absorption between 450 and 600 mμ, $\epsilon_{max.}$ 10. The band persists almost unchanged in the phenanthroline and dipyridyl complexes (Field and Roberts, *loc. cit.*), but in the cobaltous terpyridyl complex there is strong absorption over the range 400—500 mμ of extinction coefficient greater than 10^3 (Wilkins and Smith, *Analyt. Chim. Acta*, 1953, **9**, 338). The effect of substituents in terpyridyl upon the absorption closely parallels that in the corresponding ferrous complexes (*idem, ibid.*). Now, although in dipyridyl and *o*-phenanthroline complexes the cobaltous ion

exchanges very rapidly, yet in terpyridyl complexes the exchange is slow, suggesting that a change to a covalent complex has taken place, *i.e.*, a cobaltous complex involving 3*d* orbitals (West, *J.*, 1954, 578). The evidence indicates that the absorption observed in this cobaltous complex is similar to that discussed in the covalent ferrous complexes. In this connection, the cobaltous complexes of *NN'*-disalicylidene-ethylenediamine and *o*-phenylenediamine are covalent and intensely coloured, and the exchange of the cobaltous ion in them is slow (West, *J.*, 1954, 395).

Transitions of Bonding Electrons.—From the above discussion it is clear that the distinction between a bonding and a non-bonding electron will frequently be artificial. An electron not involved in bonding in the normal or ground state of the complex may become so in the excited state. Such cases have been considered under non-bonding electrons. In certain charge-transfer spectra the excited state is the only state in which a bond is formed, the normal state being a " no-bond " structure. A full discussion of these molecules and their spectra has been given by Mulliken (*J. Phys. Chem.*, 1952, **56**, 801). It is also possible in charge transfer for the excited state to be the no-bond structure, but as Bowen (*loc. cit.*) has pointed out, there will be very many other cases in which excitation will produce a modification of bonding and it is doubtful if any purpose is served by labelling all these spectra as charge-transfer bands.

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Further Studies on Unstable Optical Activity in the N-Benzoyldiphenylaminecarboxylic Acid Series.

By MARGARET M. HARRIS (née JAMISON), W. G. POTTER, and E. E. TURNER.

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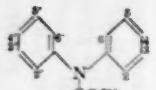
Suitably substituted *N*-benzoyldiphenylamine-2-carboxylic acids show labile optical activity, although scale models demonstrate that rotation about the three N–C bonds *can* take place when the movement of the three groups attached to nitrogen is synchronised. The relative optical stabilities of fourteen such acids are here assessed by comparison of the rate constants of racemisation and of first-order asymmetric transformations, and the dependence of optical stability upon structure is discussed. Evidence of molecular aggregation (in non-polar solvents containing alkaloids plus excess of acid) beyond that required for simple salt formation is brought forward in explanation of the fact that first-order asymmetric transformation (optical activation) at acid : base ratio 1 : 1 is often different in direction and in degree from that at other acid : base ratios.

THIS paper reports the synthesis and stereochemical examination of six acids in the *N*-benzoyldiphenylaminecarboxylic acid series to add to the ten other related acids on which some investigations have already been made (Jamison and Turner, *J.*, 1937, 1954; 1938, 1646; 1940, 264). It is now possible to draw wider comparisons which throw more light on the unstable optical activity which is characteristic of the group. Those acids in the series which show optical activity often undergo first- and second-order asymmetric transformation (defined as in *J.*, 1942, 437) of their alkaloidal salts and, in particular, several of them show optical activation to differing extents, perhaps even in reversed directions, when the alkaloid and acid are mixed in solution in varying proportions.

A range of processes, namely, racemisation and optical activation in the presence of different alkaloids, has here been used in order to assess the relative optical stabilities of this set of acids; Table 1 gives the measured values of the unimolecular rate constants.

TABLE I.



Ref. no. of acid	2	4	6	2′	4′	Racemisation k	Temp.	Solvent †	First-order asymmetric transformations: (+)-Nor-ψ-ephedrine in $CHCl_3$ k	Temp.	Ratio, acid : base	Quinidine in X at 20·0° k 1 : 1	2 : 1	3 : 1	Brucine in X at 20·0° k 1 : 1	2 : 1	Cinchonidine in X at 15·0° k 1 : 1
1	—	CO_2H	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
2	—	CO_2H	—	—	Cl	—	—	—	—	—	—	—	—	—	—	—	—
3	CO_2H	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
4	CO_2H	—	—	Cl	Cl	—	—	—	0·365 [1]	−31°	4 : 1	—	—	—	—	—	—
5	CO_2H	—	—	Me	Me	—	—	—	0·254 [1]	−30	3 : 1	—	—	—	—	—	—
6	CO_2H	—	Me	—	—	—	—	—	0·322	20	3 : 1	—	—	—	—	—	—
7	CO_2H	—	Me	Me	—	0·567	20°	X	—	—	—	0·0602	0·667	—	—	—	—
8	CO_2H	Cl	Cl	—	—	0·345 [2]	15	X	—	—	—	—	—	—	—	—	0·091 [2]
9	CO_2H	Br	Br	—	—	0·702	20	$CHCl_3$	—	—	—	—	—	—	—	—	0·0495 *
10	CO_2H	Br	Br	—	Br	0·357 [1]	17·8	$CHCl_3$	0·126 [1]	17·5	3 : 1	—	—	—	—	—	—
11	CO_2H	—	Me	F	—	0·180	20	$CHCl_3$	—	—	—	0·0339	0·243	—	—	—	—
						0·209	20	X									
12	CO_2H	—	Me	Cl	Me	0·167	20	X	—	—	—	—	0·242	0·314	0·0922	0·297	—
13	CO_2H	—	Me	Cl	—	0·147	20	X	—	—	—	0·0244 [2]	0·253	—	0·0875	—	—
14	CO_2H	—	Me	Br	—	0·115	20	X	—	—	—	0·0160	0·255	—	0·0880	—	—
15	CO_2H	—	Me	Cl	Cl	0·0929	20	X	—	—	—	0·0118	0·202	0·238	0·0555	0·185	—
16	CO_2H	—	Me	Cl	Br	0·0862	20	X	—	—	—	0·0115	0·174	0·251	0·0545	0·142	—

Values of k are in terms of $\log_e$ min.$^{-1}$. * Calc. at 15° from values at three other temps. † X = $CHCl_3$ containing 2½% of EtOH.

[1] Jamison and Turner, *J.*, 1938, 1646. [2] *Idem*, *J.*, 1940, 264.

In the graph (Fig. 1) the acids are placed in an order of optical stability which gives the best agreement with all the rate constants.

The acids (1) and (2) which have no substituent *ortho* to the nitrogen atom show no signs of optical activity. This is convincing evidence that the optical activity shown by the others is due to restricted rotation within the molecule and not to asymmetric tervalent nitrogen. Acid (3), which shows no activity by the methods listed, has already been inferred to be capable of exhibiting optical activity but to be more labile than acids (4) and (5) (Jamison and Turner, *J.*, **1938**, 1646). The remainder all show mutarotations with

FIG. 1.

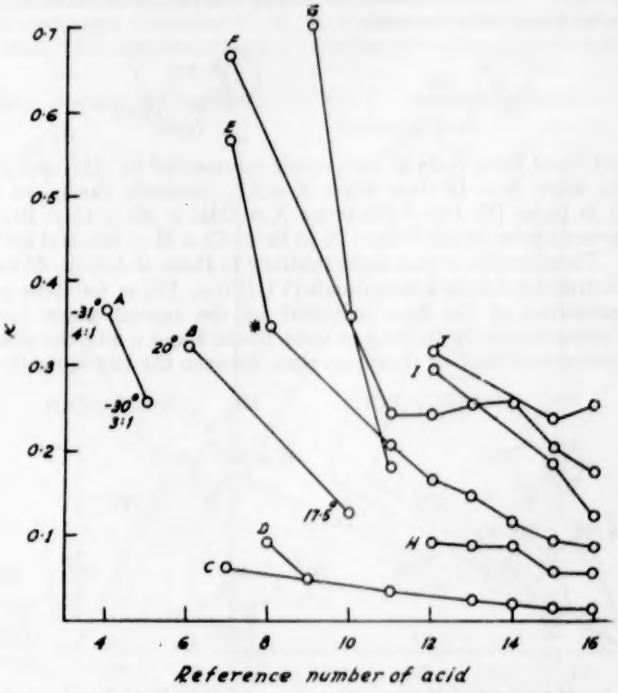


FIG. 1. *A, With (+)-nor-ψ-ephedrine,* $CHCl_3$.
B, With (+)-nor-ψ-ephedrine, $CHCl_3$, 3 : 1.
C, With quinidine, X, 1 : 1, 20°.
D, With cinchonidine, X, 1 : 1, 15°.
E, Racemisation of acid, X, 20°.
F, With quinidine, X, 2 : 1, 20°.
G, Racemisation of acid, $CHCl_3$.
H, With brucine, X, 1 : 1, 20°.
I, With brucine, X, 20°.
J, With quinidine, X, 3 : 1, 20°.
* At 15°.

at least one alkaloid in chloroform or chloroform containing 2½% of ethanol (" solvent X "); the concentration of ethanol in the chloroform has a marked effect both on the rate constants and on the extent of the mutarotations.

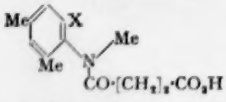
In every case in which an active acid was obtained it came from an active alkaloidal salt which was the product, not of resolution, but of second-order asymmetric transformation.

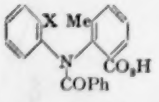
It will be noticed that the rate constants of some of the first-order transformations are less than the rate constants of racemisation of the acids involved (*e.g.*, with quinidine, cinchonidine, or brucine at acid : base ratio 1 : 1) and that some are greater (*e.g.*, with quinidine or brucine at acid : base ratio 2 : 1).

Scale models (constructed without consideration of the van der Waals envelopes

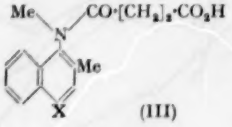
show that in even the most hindered molecules, *e.g.*, (14) and (16), rotation about all three N–C bonds is still possible, as long as there is *synchronised* movement of the various parts: this is true whether the nitrogen-atom model is taken with valencies at angles of 109° 28′ or of 120°. In the most favourable positions, rotation is unrestricted, but these "favourable rotating positions" must be relatively rarely attained.

In the series (I) investigated by Adams and his co-workers (*J. Amer. Chem. Soc.*, 1942, **64**, 1475; 1948, **70**, 2667; 1950, **72**, 2454, 2458) the decreasing order of optical stability is X = I > Br > Cl > OMe > NO_2, which they related to the basic strengths of the corresponding *o*-substituted anilines. In the present series (II) the order is X = Br > Cl > F > Me > H. It is not possible in such series to separate the bulk and the polar influences of the hindering groups. This can, however, be done by comparing the effect of *p*-substituents, which can have no direct steric influence.


(I)


(II)

Adams found in all three pairs of compounds represented by (III) and (IV) a greater optical stability when X = H than when X = Cl; similarly Buchanan and Graham (*J.*, 1950, 500) in series (V) found the order X = OMe > Me > Cl > Br. We find in series (VI) a reversed order of stabilities: X = Br > Cl > H > Me, and in (VII) stability X = Br > H. These results, at first sight contrary to those of Adams, do in fact support his work. It is true for Adams's compounds (VIII) (*i.e.*, IV) or for those now described (IX) that mesomerism of the type indicated by the curved arrow (along bond *a*) will accelerate racemisation by tending to force bonds *b* and *c* into the plane of ring A: this is the "passing position" or transition state between the two optically active forms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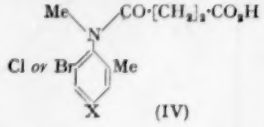
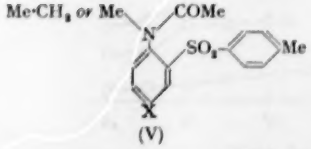
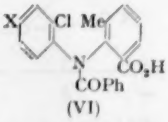

(IV)


(V)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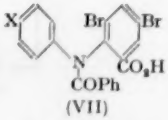
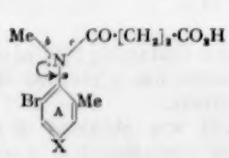
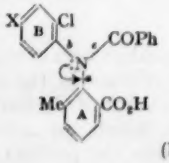

(VII)

(it is assumed for the moment that rotation is restricted about bond *a* only: if bond *b* were similarly restricted, a second centre of asymmetry would be introduced). A *p*-halogen substituent in ring A will enhance such a mesomeric process in either case, as Adams has demonstrated for types (VIII), but *p*-halogen in ring B will have two effects, both


(VIII)


(IX)

decelerating to racemisation; the mesomeric engagement of the nitrogen electrons with ring B will tend to bring bonds *a* and *c* into a plane with ring B which is then in the position for maximum interference with the *o*-groups on ring A. Bond *a* will lose its partial double character and therefore will allow the groups attached to bonds *b* and *c* to take up positions of minimum interference of the attached groups, roughly in a plane at right angles to ring A

and containing bond *a*. A methyl group, with its inductive effect in the opposite sense, in position X of (IX) will accelerate racemisation by releasing electrons for conjugation with ring A. It is relevant that the order of basic strengths of *p*-substituted anilines is Me > H > Cl > Br (Dippy, *Chem. Reviews*, 1939, **151**, 209).

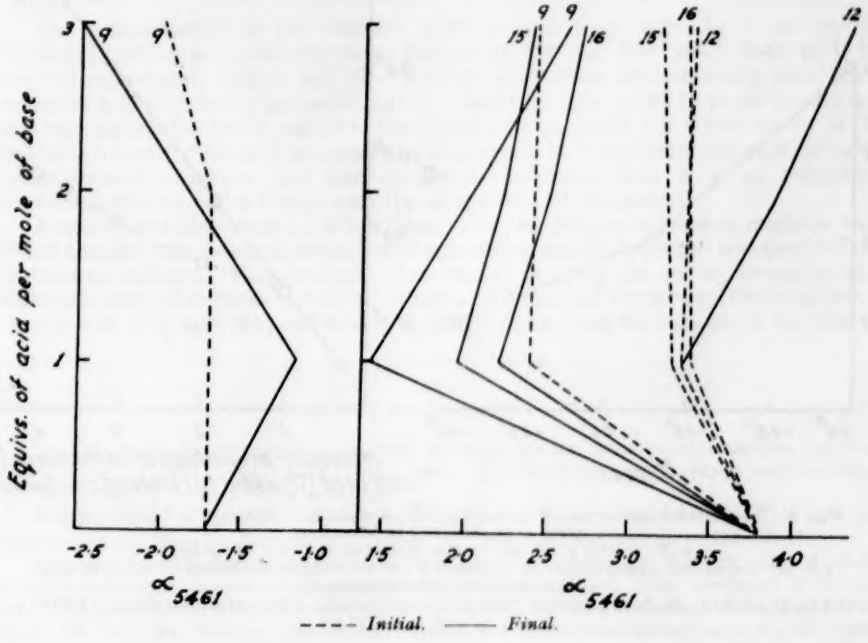
It is assumed throughout this discussion that the demand on the nitrogen electrons by the benzoyl group is constant and can therefore be disregarded in drawing comparisons.

The acid (VI; X = OMe) was synthesised in order to correlate the polar effect of the methoxyl group with the rate of racemisation, low optical stability being expected: unfortunately, this compound could not be made to undergo second-order asymmetric transformation, and so was not obtained active. Quinidine activates it, but to so small an extent that accurate kinetic measurements could not be made.

Attempts to synthesise *N*-benzoyl-2′ : 4′ : 6 : 6′-tetramethyldiphenylamine-2-carboxylic acid and *N*-benzoyl-2-bromo-6-methoxy-2′ : 6′-dimethyldiphenylamine-4-carboxylic acid

FIG. 2. *Additions to cinchonidine in solvent X.*

FIG. 3. *Additions to quinidine in solvent* X.



were abandoned owing to failure to find appropriate conditions for the Chapman rearrangement of the corresponding imidoates.

It is possible that molecules substituted in the 2-, 6-, and 2′- or 6′(or both)-positions (*e.g.*, IX) have a second centre of asymmetry, owing to restriction of rotation about bond *b* as well as about bond *a*. As the rate constants for the two racemisation processes are likely to be of a similar order of magnitude, the measured rate constant, $k = k_a + k_b$, can still be calculated according to the unimolecular law.

The second feature of particular interest in this series of compounds is the wide variation in extent and direction of first-order asymmetric transformation in presence of one equivalent or less of an optically active alkaloid. This is demonstrated in the graphs Figs. 2 and 3.

Since this phenomenon was first discovered in 1938 (Jamison and Turner, *loc. cit.*) the field of application of an " asymmetric influence " has been extended from direct chemical

combination to the operation of an asymmetric solvent (Buchanan and Graham, *loc. cit.*; Glazer, Harris, and Turner, *J.*, 1950, 1753; compare also Davies and Dwyer, *Trans. Faraday Soc.*, 1954, **50**, 24, on the operation of asymmetric influences in *aqueous* solutions). It now seems reasonable to suppose that, since an asymmetric solvent can, by some loose attachment, such as hydrogen bonding, activate a labile asymmetric molecule, a molecule of an alkaloid in solution can activate more than one equivalent of an optically labile active acid. This being so, it is not unlikely that the *second* molecule of acid "attached" to the alkaloid molecule should be subjected to influences which determine its configuration either in the same sense or in the opposite sense from the first, which is closely bound to it in salt formation.

FIG. 4.

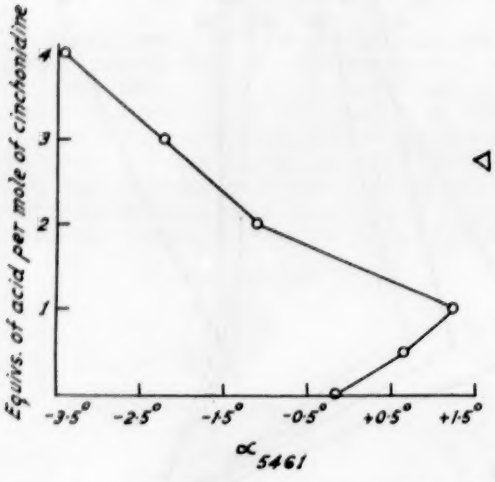


FIG. 5.

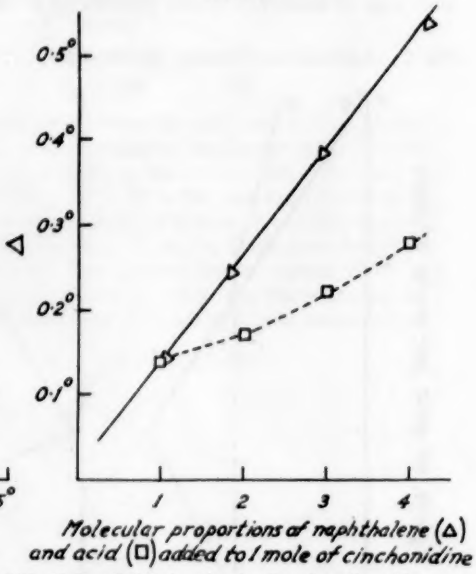


FIG. 4. *Polarimetric measurements in N-benzoyl-2′ : 4′-dimethyldiphenylamine-2-carboxylic acid added to cinchonidine in bromoform.*
(*l* = 2; 0·1000 g. of cinchonidine dissolved in 15 c.c. of $CHBr_3$.)

FIG. 5. *Cryoscopic measurements on N-benzoyl-2′ : 4′-dimethyldiphenylamine-2-carboxylic acid added to cinchonidine in bromoform.*
(At 15°, 15 c.c. of bromoform contain 0·1000 g. of cinchonidine; 1 mol. of naphthalene = 0·0435 g.; 1 mol. of acid = 0·1173 g.)

We have made preliminary experiments with a view to examining the molecular aggregation of an alkaloid with an excess of acid dissolved in non-ionising solution:

(a) *Evidence from solubility.* Solubility determinations were made in dry chloroform (free from ethanol) at 20°; 10 c.c. dissolved 0·0230 g. (0·26 mol.) of *N*-benzoyl-4′-chlorodiphenylamine-2-carboxylic acid. 10 C.c. of chloroform containing 0·0811 g. of quinine (1·00 mol.) dissolved 0·2133 g. of acid (2·42 mol.). 10 C.c. of chloroform containing 0·0986 g. of brucine (1 mol.) dissolved 0·1622 g. of acid (1·84 mol.). It is not surprising that the quinine with its second weakly basic centre should be more effective than the brucine, but both alkaloids have a considerable influence in increasing the solubility of the acid.

(b) *Evidence from freezing-point depressions in bromoform.* Bromoform was chosen as cryoscopic solvent for our investigations because it was thought that the behaviour of the alkaloid and acids in that solvent would parallel closely the behaviour in chloroform, which

we have used widely for stereochemical experiments. Accordingly an " addition curve " was plotted, by adding successive quantities of *N*-benzoyl-2' : 4'-dimethyldiphenylamine-2-carboxylic acid (5) to a constant amount of cinchonidine dissolved in bromoform and reading the optical rotation of each solution : no mutarotation was detectable at room temperature. The result is plotted in Fig. 4. Next, cryoscopic measurements were made on a similar set of solutions : the results are plotted in Fig. 5, with freezing-point depressions for naphthalene as a standard. Difficulty was experienced with the bromoform, which could seldom be kept, even for a few hours after purification by vacuum-distillation and by freezing, without its beginning to darken. It was not satisfactory to add ethanol, as this would have masked the depression due to the added substances : solutions which darkened were immediately discarded. However, it was found that solutions did not darken once the cinchonidine was added, and therefore if this stage was reached quickly a satisfactory set of determinations could be made. It will be seen that the depression for two molecules of acid and one of cinchonidine is only slightly larger than that for one molecule of either, and that there is also evidence of very considerable molecular aggregation at four molecules of acid.

The precise nature of the cohesive forces in such large molecules is not certain. Hydrogen bonding is a possibility, or, as Maryott (*J. Res. Nat. Bur. Stand.*, **1948**, **41**, 1) has pointed out, organic salts in non-polar solvents are entities with unusually large dipole moments held together by coulombic forces. Such structures would be prone to associate, and such association might well be to some extent stereospecific. It is noteworthy in this connection that the *extent* of mutarotation of mixtures of *N*-benzoyl-2'-chloro-6-methyldiphenylamine-2-carboxylic acid and quinidine (molecular ratio 2 : 1) in chloroform containing ethanol varies largely with the composition of the solvent.

Kaufman and Singleterry (*J. Phys. Chem.*, 1952, **56**, 604), by cryoscopic methods, have found a similar association of, among other substances, myristic acid and tri*iso*pentylamine in benzene solution. They interpret their results as being due to the formation of a molecular complex between the amine and an acid dimer and the existence of equilibria of the types $N + A_2 \rightleftarrows NA_2$ and $NA_2 + A_2 \rightleftarrows NA_4$, N being the base and A the acid.

Experimental

The diphenylaminecarboxylic acids were prepared by the same general method (Jamison and Turner, *J.*, **1937**, **1954**; **1938**, **1646**; **1940**, 264) involving the Chapman rearrangement (*J.*, **1929**, 569) of corresponding imidoates.

Preparation of N-*Benzoyl-2'* : 6-*dimethyldiphenylamine-2-carboxylic Acid* (7).—This acid was prepared as described by Jamison and Turner (*J.*, 1940, 264) and had m. p. **183—184°**.

Preparation of N-*Benzoyl-4* : 6-*dibromodiphenylamine-2-carboxylic Acid* (9).—(a) 4 : 6-*Dibromo-2-methoxycarbonylphenyl* N-*phenylbenzimidoate* crystallised from methanol in prisms, m. p. 102—103° (yield 86%) (Found : C, 51·4; H, 3·1; Br, 32·5. $C_{21}H_{15}O_3NBr_2$ requires C, 51·5; H, 3·3; Br, 32·6%). (b) *Methyl* N-*benzoyl-4* : 6-*dibromodiphenylamine-2-carboxylate*. The imidic ester underwent rearrangement at 190—200°; the *product* (yield 80%) crystallised from methanol in prisms, m. p. **134—135°** (Found : C, 51·3; H, 4·0; Br, 32·7. $C_{21}H_{15}O_3NBr_2$ requires C, 51·5; H, 3·3; Br, 32·6%). (c) N-*Benzoyl-4* : 6-*dibromodiphenylamine-2-carboxylic acid* crystallised in a solvated form from ethanol, but from benzene gave microcrystals, m. p. 189—190° (Found : C, 50·9; H, 2·9. $C_{20}H_{13}O_3NBr_2$ requires C, 50·5; H, 2·7%).

No mutarotation was observed with the (±)-acid and either brucine or cinchonidine in solvent X at acid : base ratio 1 : 1.

The *cinchonidine* (+)-*acid* salt (Table 2, p. 153) (Found : C, 61·2; H, 4·6; Br, 19·5. $C_{39}H_{35}Br_2O_4N_3$ requires C, 60·9; H, 4·6; Br, 20·8%) mutarotated in solvent X, $c = 0·7600$, k 0·193 at 27·3°, 0·096 at 20·7°, 0·060 at 16·7°, 0·029 at 10·8° [Found for (+)-*acid* : Br, 32·9. $C_{20}H_{13}O_3NBr_2$ requires 33·6%].

Preparation of N-*Benzoyl-2'-fluoro-6-methyldiphenylamine-2-carboxylic Acid* (11).—(*a*) *o*-Fluoroaniline (77%; b. p. **104—106°/56** mm.) was prepared from *o*-fluorobenzoic acid by the Schmidt reaction (Minor and Van der Werf, *J. Org. Chem.*, **1952**, **17**, 1425). Air was excluded from the reaction vessel by a stream of nitrogen. *Benzo-o-fluoroanilide* crystallised from ethanol

and had m. p. 113° (Found: C, 72·25; H, 5·1. $C_{13}H_{10}ONF$ requires C, 72·2; H, 5·1%). (*b*) *N-o*-Fluorophenylbenzimidoyl chloride, b. p. 196—200°/27 mm., condensed with methyl 2-hydroxy-3-methylbenzoate in the presence of sodium ethoxide to give a 61% yield of *2-methoxycarbonyl-6-methylphenyl* N-*o-fluorophenylbenzimidoate* which crystallised from light petroleum (b. p. 40—60°) in prisms, m. p. 58—60° (Found: C, 72·7; H, 4·2. $C_{22}H_{18}O_3NF$ requires C, 72·7; H, 5·0%). (*c*) *Methyl* N-*benzoyl-2'-fluoro-6-methyldiphenylamine-2-carboxylate*. The imidoate isomerised at 275° to give an 81% yield of *diphenylamine ester*, which crystallised from methanol in prisms, m. p. 104—106° (Found: C, 72·5; H, 4·8. $C_{22}H_{18}O_3NF$ requires C, 72·7; H, 5·0%). (*d*) N-*Benzoyl-2'-fluoro-6-methyldiphenylamine-2-carboxylic acid*. The ester was hydrolysed with aqueous alcoholic sodium hydroxide, and the acid dissolved in sodium hydrogen carbonate solution, reprecipitated, washed, and dried by azeotropic distillation of the last traces of water with benzene; repeated crystallisation from acetone–benzene gave an *acid* of constant m. p. 187—188° (Found: C, 72·8; H, 4·0. $C_{21}H_{16}O_3NF$ requires C, 72·2; H, 4·6%). Decomposition of the *brucine* (−)-*acid* salt (Found: C, 71·0; H, 6·2. $C_{44}H_{42}O_7N_3F$ requires C, 71·0; H, 5·7%) gave the (−)-acid.

Preparation of N-*Benzoyl-2'-chloro-4'*: *6-dimethyldiphenylamine-2-carboxylic Acid* (12).—(a) *2-Methoxycarbonyl-6-methylphenyl* N-*2'-chloro-4'-methylphenylbenzimidoate*. Equimolecular amounts of methyl 2-hydroxy-3-methylbenzoate and *N*-2-chloro-4-methylphenylbenzimidoyl chloride were condensed in the presence of sodium ethoxide. The resulting *imidoate* crystallised from methanol in prisms, m. p. 113—114° (Found: C, 69·1; H, 5·3. $C_{23}H_{20}O_3NCl$ requires C, 70·1; H, 5·1%). (b) *Methyl* N-*benzoyl-2'-chloro-4'*: *6-dimethyldiphenylamine-2-carboxylate* was prepared by rearrangement of the imidoate at 285—290°; it crystallised from methanol in prisms, m. p. 187—188° (79% yield) (Found: C, 70·3; H, 5·0. $C_{23}H_{20}O_3NCl$ requires C, 70·1; H, 5·1%). (c) N-*Benzoyl-2'-chloro-4'*: *6-dimethyldiphenylamine-2-carboxylic acid* was purified through solution in dilute sodium hydrogen carbonate, and recrystallisation from benzene and then from benzene–acetone; it had m. p. 210—211° (Found: C, 69·6; H, 4·7; Cl, 8·9. $C_{22}H_{18}O_3NCl$ requires C, 69·6; H, 4·8; Cl, 9·3%). Decomposition of the *brucine* (−)-*acid* salt (Found: C, 69·7; H, 5·7. $C_{46}H_{46}O_7N_3Cl$ requires C, 69·8; H, 5·3%) gave the (−)-acid.

Preparation of N-*Benzoyl-2'-chloro-6-methyldiphenylamine-2-carboxylic Acid* (13).—This acid was prepared as described by Jamison and Turner (*J.*, 1940, 264). It crystallised from acetone in slender needles, m. p. 197°.

Preparation of N-*Benzoyl-2'-bromo-6-methyldiphenylamine-2-carboxylic Acid* (14).—(a) *2-Methoxycarbonyl-6-methylphenyl* N-*o-bromophenylbenzimidoate* crystallised from methanol in prisms, m. p. 100—102° (Found: C, 62·7; H, 4·5. $C_{22}H_{18}O_3NBr$ requires C, 62·4; H, 4·3%). (b) The imidoate isomerised at 280°, giving *methyl* N-*benzoyl-2'-bromo-6-methyldiphenylamine-2-carboxylate*, which crystallised from ethanol in prisms, m. p. 191° (80% yield) (Found: C, 63·1; H, 4·3. $C_{22}H_{18}O_3NBr$ requires C, 62·4; H, 4·3%). (c) N-*Benzoyl-2'-bromo-6-methyldiphenylamine-2-carboxylic acid* was crystallised from ethanol and then from benzene and had m. p. 198—199° which varied with the rate of heating (Found: C, 61·9; H, 4·1. $C_{21}H_{16}O_3NBr$ requires C, 61·4; H, 3·9%). The brucine salt of the (−)-acid mutarotated in solvent X at 20·0° from −4·63° to −0·30° in 31 min. (*c*, 0·8000).

Preparaton of N-*Benzoyl-2'*: *4'-dichloro-6-methyldiphenylamine-2-carboxylic Acid* (15).—(a) *2-Methoxycarbonyl-6-methylphenyl* N-(*2*: *4-dichlorophenyl*)*benzimidoate* crystallised from methanol in prisms, m. p. 74—76°, in 69% yield (Found: C, 63·5; H, 4·2. $C_{22}H_{17}O_3NCl_2$ requires C, 63·8; H, 4·1%). (b) *Methyl* N-*benzoyl-2'*: *4'-dichloro-6-methyldiphenylamine-2-carboxylate*. The imidoate underwent Chapman's rearrangement at 285—290° (70% yield); the *product* crystallised from methanol in prisms, m. p. 131—133° (Found: C, 63·25; H, 4·15. $C_{22}H_{17}O_3NCl_2$ requires C, 63·8; H, 4·1%). (c) N-*Benzoyl-2'*: *4'-dichloro-6-methyldiphenylamine-2-carboxylic acid* was purified through its sodium salt, washed with hot water, and crystallised from benzene–acetone; it had m. p. 201—202° (Found: Cl, 17·2. $C_{21}H_{15}O_3NCl_2$ requires Cl, 17·7%). Decomposition of the brucine (−)-acid salt gave the (−)-acid.

Preparation of N-*Benzoyl-4'-bromo-2'-chloro-6-methyldiphenylamine-2-carboxylic Acid* (16).—(a) *2-Methoxycarbonyl-6-methylphenyl* N-(*4-bromo-2-chlorophenyl*)*benzimidoate* crystallised from ethanol in prisms, m. p. 87—88° (Found: C, 56·9; H, 3·7. $C_{22}H_{17}O_3NBrCl$ requires C, 57·6; H, 3·7%). (b) *Methyl* N-*benzoyl-4'-bromo-2'-chloro-6-methyldiphenylamine-2-carboxylate*. Rearrangement of the benzimidoate at 275° gave the *diphenylamine* ester in 83% yield, as prisms, m. p. 138° (Found: C, 57·7; H, 3·8. $C_{22}H_{17}O_3NBrCl$ requires C, 57·6; H, 3·7%). (c) N-*Benzoyl-4'-bromo-2'-chloro-6-methyldiphenylamine-2-carboxylic acid*. The ester was hydrolysed by aqueous alcoholic sodium hydroxide; the *acid*, after purification through the sodium salt

and crystallisation from benzene–acetone, had m. p. 186—187°, varying with the rate of heating (Found: mixed halogen, 25·3. $C_{21}H_{15}O_3NBrCl$ requires mixed halogen, 25·9%). Decomposition of the *brucine* (−)-*acid* salt (Found: C, 61·3; H, 5·2. $C_{44}H_{41}O_7N_3BrCl$ requires C, 61·6; H, 4·8%) gave the (−)-acid.

Preparation of N-Benzoyl-2′-chloro-4′-methoxy-6-methyldiphenylamine-2-carboxylic Acid.—(*a*) *N*-(2-Chloro-4-methoxyphenyl)benzimidoyl chloride (crude) was condensed with methyl 2-hydroxy-3-methylbenzoate to give *2-methoxycarbonyl-6-methylphenyl N-(2-chloro-4-methoxyphenyl)benzimidoate*, prisms (from methanol), m. p. 94—95° (Found: C, 66·8; H, 4·5. $C_{23}H_{20}O_4NCl$ requires C, 67·4; H, 4·9%). (*b*) The imidoate underwent rearrangement at 285° (0·5 hr.) to give 82% yield of *methyl N-benzoyl-2′-chloro-4′-methoxy-6-methyldiphenylamine-2-carboxylate*, prisms (from methanol), m. p. 124—125° (Found: C, 67·6; H, 4·9. $C_{23}H_{20}O_4NCl$ requires C, 67·4; H, 4·9%). (*c*) Hydrolysis of this *ester* with the calculated quantity of aqueous-alcoholic sodium hydroxide gave *N-benzoyl-2′-chloro-4′-methoxy-6-methyldiphenylamine-2-carboxylic acid* which crystallised from benzene–acetone and had m. p. 214—215° (Found: C, 66·8; H, 4·65. $C_{22}H_{18}O_4NCl$ requires C, 66·6; H, 4·6%). This acid did not undergo second-order asymmetric transformation with brucine in a wide range of solvents.

Attempted Preparation of 2′ : 4′ : 6 : 6′-Tetramethyldiphenylamine-2-carboxylic Acid.—(*a*) *N*-(2 : 4 : 6-Trimethylphenyl)benzimidoyl chloride (b. p. 192—195°/15 mm.) was condensed with methyl 2-hydroxy-3-methylbenzoate to give *2-methoxycarbonyl-6-methylphenyl N-(2 : 4 · 6-trimethylphenyl)benzimidoate*, as prisms, m. p. 83—85°, from methanol (Found: C, 77·3; H, 6·6. $C_{24}H_{23}O_3N$ requires C, 76·8; H, 5·9). Attempts to cause isomerisation of this to the corresponding diphenylamine derivative resulted either in recovery of the original material or in a tar.

Attempted Preparation of N-Benzoyl-2-bromo-6-methoxy-2′ : 6′-dimethyldiphenylamine-4-carboxylic Acid.—(*a*) *Methyl 3-bromo-4-hydroxy-5-methoxybenzoate*, m. p. 155—156°, was prepared from the acid by Fischer–Speier esterification (Found: C, 41·95; H, 3·7. $C_9H_9O_4Br$ requires C, 41·4; H, 3·5%). Condensation with *N*-(2 : 4-dimethylphenyl)benzimidoyl chloride gave *2-bromo-6-methoxy-4-methoxycarbonylphenyl N-(2 : 6-dimethylphenyl)benzimidoate* (61%), m. p. 162—164° (Found: C, 61·9; H, 4·8. $C_{24}H_{22}O_4NBr$ requires C, 61·5; H, 4·7%). Attempts to induce the Chapman rearrangement failed; tars were obtained.

Polarimetric Measurements.—These were carried out in a 2-dm. jacketed tube, thermostatically controlled; λ_{5461} was used throughout; rate constants are in terms of natural logarithms and min.$^{-1}$.

" Solvent X."—" B.P." chloroform was washed, dried, and distilled, and 2·5% by volume of ethanol was added.

Anhydrous Brucine.—See Turner, *J.*, 1951, 842.

Anhydrous Quinidine.—Quinidine crystallised from benzene was dried in a vacuum at 100° over phosphoric oxide: it had $[\alpha]_{5461}^{20}$ +301·1° in solvent X (*c*, 0·8000).

Chloroform for polarimetric experiments was washed free from ethanol and dried.

Second-order Asymmetric Transformations.—(±)-Acid and alkaloid were used in equimolecular proportions dissolved separately and then mixed; crystallisation took place at room temperature or higher: chilling was avoided as it would slow down the partial inversion of the diastereoisomers in solution.

Results are in Table 2. The number of the acid refers to Table 1.

TABLE 2.

(±)-Acid	Alkaloid	Solvent *	Salt crystallising	Yield (%)	Acid obtained from salt
7	Brucine	$COMe_2$–Pet	B–(−)-Acid	87	(−)
9	Cinchonidine	$COMe_2$–Et_2O	B–(+)-Acid	86	(+)
11	Brucine	$COMe_2$	B–(−)-Acid	90	(−)
12	Brucine	EtOH–Et_2O	B–(−)-Acid	92	(−)
14	Brucine	,,	B–(−)-Acid	91	(−)
15	Brucine	$COMe_2$–Pet	B–(−)-Acid	87	(−)
16	Brucine	,,	B–(−)-Acid	83	(−)

* Pet. = light petroleum (b. p. 40—60°).

The active acids were obtained by grinding the salts with cold, anhydrous formic acid, and filtering the solutions from any undissolved particles of salt directly into dilute hydrochloric acid and ice. The precipitated acids were washed with water and dried in a vacuum.

For details of other kinetic results see Tables 3—5.

TABLE 3. *Racemisation of optically active acids* (*c*, 0·4000; *temp.*, 20°).

Acid	Initial reading: α	Initial reading: Time after dissoln. (min.)	Solvent	*k*	Limits of *k*	
7	−0·23°	3·5	X	0·57	0·53	0·61
9	+0·42	1·85	$CHCl_3$	0·70	0·67	0·73
11	−0·28	1·3	$CHCl_3$	0·18	0·16	0·22
	−2·41	2·52	X	0·21	0·205	0·21
12	−2·74	3·35	X	0·17	0·165	0·17
14	−2·91	2·45	X	0·115	0·11	0·12
15	−2·27	3·95	X	0·092	0·0905	0·094
16	−2·57	3·05	X	0·086	0·084	0·088

TABLE 4. *First-order asymmetric transformations.*

Solvent X; temp., 20·0°; brucine, $c = 0·7880$; cinchonidine, $c = 0·5880$; quinidine, $c = 0·6480$, unless marked * when $c = 0·8100$; (+)-nor-ψ-ephedrine, $c = 0·5000$.

(±)-Acid	Mols. acid per mol. base	Alkaloid ‡	Time (min.) of initial reading after mixing	Initial reading	Final reading
6 †	3	(+)-Nor-ψ-ephedrine	0·8	+0·04°	+0·70°
7	1	Quinidine	1·8	+3·29	+2·73
7	2	,,	3·1	+2·96	+2·82
9	1	,,	4·65	+2·33	+1·41
9	2	,,	3·4	+2·19	+2·02
9	1	Cinchonidine	2·85	−1·68	−1·23
9	2	,,	4·87	−1·78	−1·91
11	1	Quinidine	2·05	+2·83	+1·52
11 *	2	,,	0·8	+2·10	+1·31
12 *	2	,,	1·1	+2·72	+2·94
12	3	,,	2·55	+3·95	+4·35
12	1	Brucine	2·4	−0·40	−0·04
12	2	,,	2·5	−0·35	−0·17
13	1	Quinidine	2·5	+3·34	+2·35
13	2	,,	2·5	+3·10	+2·64
14	1	,,	3·05	+3·80	+3·01
14 *	2	,,	0·07	+2·73	+2·40
15	1	,,	2·85	+3·27	+2·00
15 *	2	,,	1·0	+2·38	+1·67
15	3	,,	3·4	+2·81	+2·44
15	1	Brucine	3·15	−0·43	−0·06
15	2	,,	2·0	−0·24	−0·07
16	1	Quinidine	2·15	+3·39	+2·25
16 *	2	,,	0·8	+2·50	+1·89
16	3	,,	3·2	+3·05	+2·74
16	1	Brucine	3·2	−0·43	−0·05
16	2	,,	3·15	−0·19	−0·07

† Solvent $CHCl_3$ in this case.

TABLE 5. *Variation of extent of first-order asymmetric transformation of* N-*benzoyl-2′-chloro-6-methyldiphenylamine-2-carboxylic acid with quinidine* (2 : 1) *in* $CHCl_3$–EtOH *at* 20°.

(25 C.c. of solution contain 0·1620 g. of quinidine and 0·3657 g. of acid.)

Ethanol (%) in chloroform	Time of first reading after dissoln. (min.)	First reading	Final reading	Extent of mutarotation (α_0 by extrapolation − α_∞)
0·0	4·06	+3·05°	+2·90°	0·26°
1·0	2·65	3·02	2·78	0·43
2·5	2·5	3·10	2·64	1·09
3·2	4·2	2·91	2·58	0·87
6·0	2·6	3·23	2·73	0·87
9·1	3·34	3·26	2·79	0·87
17·0	4·00	3·35	3·00	0·75
30·0	4·1	3·49	3·20	0·59
50·0	3·66	3·62	3·42	0·32
100·0	3·73	1·84	1·84	0·0

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BEDFORD COLLEGE, UNIVERSITY OF LONDON. [*Received, July 21st,* 1954.]

The Determination of the Isotopic Composition of the Oxygen in Alcohols and Related Compounds.

By M. Anbar, I. Dostrovsky, F. Klein, and David Samuel.

[Reprint Order No. 5642.]

Two general methods for the isotopic analysis of oxygen in organic compounds are described briefly. A simpler method, but more limited in its application, is described fully. This is based upon the establishment of an isotopic equilibrium between the oxygen atom of an alcohol and carbon dioxide when the two are heated in a sealed tube with a little sulphuric acid. The conditions necessary for the analysis of various classes of alcohols are indicated, and the application of the method to 25 compounds is described.

One of the main difficulties in the use of oxygen-labelled compounds in the study of organic reactions has been the isotopic analysis of the oxygen in the reactants and products. Some compounds may be analysed by introducing them directly into a mass spectrometer, but only in a few cases has such a procedure been attempted (*e.g.*, Long and Friedman, *J. Amer. Chem. Soc.*, 1950, **72**, 3692). In addition to the trouble caused by the absorption of the sample in the inlet and other parts of the mass spectrometer, the considerable fragmentation, which occurs upon ionisation, makes the interpretation of the mass spectrum difficult. It is, therefore, always preferable to transfer the oxygen atoms of the organic molecule to another simpler molecule, such as carbon dioxide or oxygen, which can be purified before introduction into the mass spectrometer.

In an adaptation of Ter Meulen's procedure for the analysis of oxygen in organic compounds (Elving and Ligett, *Chem. Reviews*, 1944, **34**, 129; Russell and Fulton, *Ind. Eng. Chem., Anal.*, 1933, **5**, 384), the sample is pyrolysed over a catalyst in a stream of hydrogen, and the cracked material is then passed over a hydrogenation catalyst. The water produced is collected and analysed for its isotopic oxygen content (Dostrovsky and Klein, *Analyt. Chem.*, 1952, **24**, 414). The main difficulty with this method lies in the considerable " memory " effect (*i.e.*, contamination of one sample by traces of a previous sample) which occurs mostly in the pyrolysis chamber. By replacing this chamber by one made of platinum and filled with platinum gauze, and introducing a liquid-air trap between pyrolysis and reduction sections of the apparatus, a considerable reduction in the " memory " effect is obtained. Nevertheless the procedure is time-consuming and requires relatively large amounts of material, particularly since, in order to minimise " memory " effects, several samples have to be processed before a final analysis is made.

An adaptation of Unterzaucher's procedure for oxygen determination (cf. Harris, Smith, and Mitchell, *ibid.*, 1950, **22**, 1297) was investigated. Pyrolysis was carried out in a vacuum-system without a carrier, the condensable compound frozen out with liquid air, and the hydrogen removed by pumping through a heated palladium tube. The remaining carbon monoxide was either introduced directly into the mass spectrometer, or converted catalytically over nickel into carbon dioxide. This method is again rather lengthy, and the isotopic contamination due to the silica surfaces and the granulated carbon is considerable (see, however, Doering and Dorfman, *J. Amer. Chem. Soc.*, 1953, **75**, 5595).

Numerous other attempts by the authors to develop a method of general applicability for the isotopic analysis of oxygen in organic compounds have not been quite satisfactory. However, a convenient and simple procedure applicable mainly to alcohols has been devised. Since alcohols themselves are often products of reactions where oxygen isotopes can be used, or may easily be formed from a number of other materials, the procedure described below has a wide field of application.

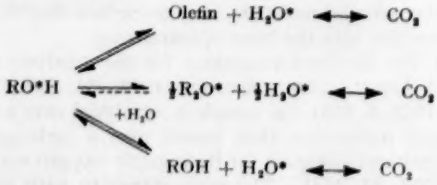
The procedure is based on the isotopic equilibration of carbon dioxide and the oxygen in the material tested, through the agency of water. The water may either be a product of decomposition of the material tested, or be in isotopic equilibrium with it. It follows that the method is limited to those substances which can undergo either partial reversible

or complete and irreversible dehydration, and also those which can exchange oxygen with water directly. These classes include alcohols, ketones, aldehydes, and carboxylic acids.

Although water exchanges its oxygen readily with carbon dioxide even at room temperature (Mills and Urey, *J. Amer. Chem. Soc.*, 1940, **62**, 1019; Reid and Urey, *J. Chem. Phys.*, 1943, **11**, 403) the dehydration reactions of organic compounds, and the oxygen-exchange reaction between them and water require higher temperatures and the presence of catalysts. The equilibration is therefore carried out by heating the sample (about 1 mmole) in a small sealed tube together with a trace of sulphuric acid (0·001 ml.) and carbon dioxide (0·05 mmole). After the mixture has been heated for a few hours at 150—200°, depending on its nature, the tube is transferred to the gas inlet system of the mass spectrometer, and the carbon dioxide analysed for its ^{18}O content.

Alcohols vary greatly in their ease of dehydration and exchange of oxygen with water. These differences are closely related to differences in the mechanism of the reactions and will be reported elsewhere (Dostrovsky and Klein). Thus the tertiary alcohols listed in the Table (p. 159) gave complete equilibrium in 1 hr. at 150°. The secondary alcohols listed gave good results after 3 hr. at 170°. Primary aliphatic alcohols, heated to 200° for 1 hr., tend to form ethers which undergo further reaction very slowly. For this reason, only half the oxygen atoms of such alcohols are readily available for exchange. Exceptions are ethyl and benzyl alcohol, which undergo almost complete exchange in 3 hr. at this temperature, and *neo*pentyl alcohol, which does not undergo ether formation but requires heating at 230° for 3 hr. for complete dehydration.

The various possible modes of reaction of an alcohol are:



In most cases, the carbon dioxide reaches isotopic equilibrium with the water, produced by any of the mechanisms described above, much faster than either the rate of formation of the water or its rate of exchange with the alcohol. Exceptions are those cases which require high temperatures for decomposition. At a temperature above 200° and with the size of sealed tube used, the small amount of water formed is almost completely volatilised. In addition, the solubility of carbon dioxide in water at this temperature is very small. Since the exchange between carbon dioxide and water under these conditions proceeds only in the liquid phase (Klein, unpublished results), the rate of the equilibration reaction may become very slow and limiting. For this reason, in all analyses involving heating above 180°, a second heat treatment is given at a lower temperature, which ensures complete isotopic equilibrium between the water and carbon dioxide. For the same reason the size of the sealed tube should be as small as possible. Sealed tubes of 1·2 ml. volume were used successfully in this work.

Because of the high ratio of the amounts of alcohol to carbon dioxide taken for the analysis, the final concentration of ^{18}O in the latter material is not very sensitive to the extent of exchange of the alcohol. Thus, if only half the oxygen atoms of an alcohol undergo exchange (as in complete ether formation), the ^{18}O concentration of the carbon dioxide is 92% of its value for complete statistical equilibrium. If the extent of oxygen exchange is now raised to 60% by further heating, the ^{18}O concentration in the carbon dioxide rises to 94% of its maximum possible value. Therefore, when an accuracy of a few units % is sufficient in the isotopic analysis of a primary alcohol, it is immaterial what the extent of alcohol oxygen exchange is, provided it is over 50%. The method can be made even less sensitive to the extent of alcohol decomposition or exchange, by using larger samples and smaller quantities of carbon dioxide, though such a procedure increases the danger of spurious results caused by impurities in the alcohol.

In most tracer work, where a precison of only a few units % is required, it is sufficient to compute the isotopic composition of the alcohol by using the ordinary dilution formula and ignoring isotope effects; thus,

$$N - N_0 = (n_1 - n_0)(m_1 + m_2 + m_3)/m_1 \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where $N - N_0$ is the atom fraction excess of ^{18}O in the alcohol and $n_1 - n_0$ is that in carbon dioxide after equilibration, and m_1, m_2, m_3 are the number of equivalents (with respect to oxygen atoms) of alcohol, carbon dioxide, and sulphuric acid respectively. The validity of equation (1) for various alcohols may be judged from the data of col. 4 in the Table.

For accurate work it is necessary to take into account, not only the dilution of the isotope, but also the equilibrium constants of the carbon dioxide and water exchange reactions at various temperatures and the equilibrium constants which may be involved in the water–alcohol exchange. In addition, allowance must be made for incompleteness of equilibrium, particularly in the case of primary alcohols. Rather than estimating these correcting factors separately, an experimental procedure was developed which eliminates all possible errors of this kind. It is only essential that the conditions of the measurements are accurately reproducible. For each alcohol two calibrating experiments are necessary where alcohol of normal isotopic composition is subjected to the analytical procedure described above, using in one case carbon dioxide of known composition n_L and in the second of known composition n_H.

The general equations relating to these experiments are :

$$N_0m_1 + n_Lm_2 + N_3m_3 = (f_1m_1 + m_2 + f_3m_3)n_1 \quad . \quad . \quad . \quad . \quad (2)$$

$$N_0m_1 + n_Hm_2 + N_3m_3 = (f_1m_2 + m_2 + f_3m_3)n_2 \quad . \quad . \quad . \quad . \quad (3)$$

Subtracting (2) from (3), we obtain

$$(n_H - n_L)m_2 = (f_1m_1 + m_2 + f_3m_3)(n_2 - n_1) \quad . \quad . \quad . \quad . \quad (4)$$

where N_0 and N_3 are the atom fractions of ^{18}O in the alcohol and sulphuric acid respectively, and n_1 and n_2 are the atom fractions of ^{18}O in the carbon dioxide from the two calibration experiments; f_1 and f_2 are correcting factors which take into account isotope effects, incomplete exchange, and lack of equilibrium.

If now an alcohol of isotopic composition N_x is analysed under identical conditions, using carbon dioxide of composition n_L, we have :

$$N_xm_1 + n_Lm_2 + N_3m_3 = (f_1m_1 + m_2 + f_3m_3)n_x \quad . \quad . \quad . \quad . \quad (5)$$

Subtracting again (2) from (5) and dividing the result by equation (4) we obtain :

$$N_x - N_0 = m_2(n_x - n_1)(n_H - n_L)/m_1(n_2 - n_1) \quad . \quad . \quad . \quad . \quad (6)$$

Equation (6) expresses the atom fraction excess of ^{18}O in the unknown alcohol in terms of easily measurable quantities, m_1, m_2, the number of equivalents of alcohol and carbon dioxide used, and the composition of the carbon dioxide before and after equilibration; n_L is usually tank carbon dioxide and n_H a standard sample of " heavy " carbon dioxide and therefore $n_H - n_L$ is, in practice, a constant. It follows that $n_2 - n_1$ is also a constant for any given alcohol. The atom fraction of ^{18}O in the carbon dioxide may be calculated from the relation $n = r/2(r + 1)$, where r is the ratio of mass 46 to 44 as obtained from the mass spectrometer and corrected for instrumental and other factors.

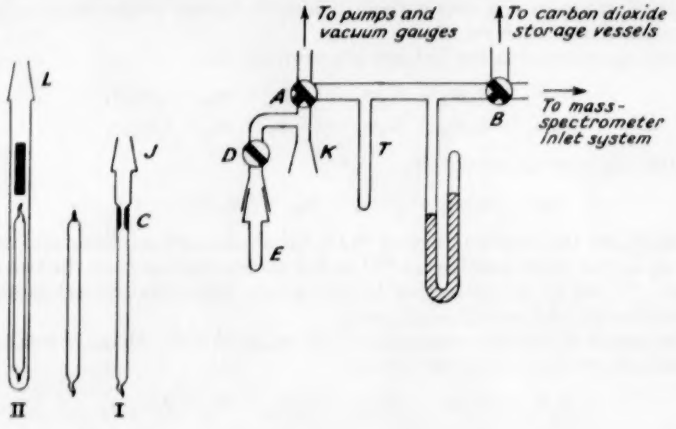
In addition to the monohydroxylic alcohols mentioned above, a number of more complicated alcohols and other oxygen-containing organic compounds were tested. Glycerol could be analysed under the usual conditions for primary alcohols, but mannitol gave only 50% exchange at 200° in 3 hr. and cholesterol only 30% under the same conditions. Phenol did not exchange its oxygen even in 3 hours at 200°. Methanol could not be analysed satisfactorily by this procedure for, although it forms an ether very readily, it is difficult to separate the dimethyl ether from the carbon dioxide. Since this ether gives a strong peak at mass 46 when introduced into a mass spectrometer, even traces of this

material can completely vitiate the result of the isotopic analysis. Methanol has been analysed very satisfactorily by Ter Meulen's procedure described above (Dostrovsky, unpublished results). Bunton and Frei (*J.*, 1951, 1872) have used the same procedure for the analysis of phenol.

Triphenylmethanol failed to give good results even when heated for 3 hr. at 206°. This compound can, however, be readily analysed for its oxygen isotope content by conversion of a small sample in benzene solution into triphenylmethyl chloride and water by means of a stream of dry hydrogen chloride (for experimental details see Anbar, Dostrovsky, Samuel, and Yoffe, *J.*, 1954, 3603).

Acetone was decomposed after 3 hr. at 180° and gave almost complete oxygen exchange with the carbon dioxide. Acetonylacetone behaves similarly when heated to 200° for 3 hr. Aldehydes and ketones which are not pyrolysed so readily can be analysed by adding a known amount of water to the contents of the sealed tube. Alternatively, such substances may be reduced to the corresponding alcohols by means of lithium aluminium hydride (Samuel, unpublished results) without change in the isotopic content.

Di-*n*-butyl ether does not equilibrate with carbon dioxide during 1 hr. at 200°. *n*-Butyl acetate does not exchange under the same conditions, but carboxylic esters and acids can be reduced to alcohols by lithium aluminium hydride and analysed in the usual way.



Experimental

Filling of Tubes.—The tubes, made from borosilicate glass tubing of 5 mm. inner diameter, have the shape shown as I in the Fig. A known quantity of concentrated sulphuric acid (0·001 ml.) is introduced into a tube by means of a micropipette and is followed by 1 mmole of the alcohol to be analysed, delivered from a micrometer syringe. Solid alcohols are weighed in the tubes before constriction *C* is made. The tube is then attached to a vacuum-line by means of the standard joints *J* and *K*, and the contents are frozen by cooling with liquid air. The tube is pumped out and, after the stopcock *A* has been closed, the contents are allowed to warm. The tube is again cooled in liquid air and evacuated once more. A small amount of pure carbon dioxide (0·05 mmole) is measured between stopcocks *A* and *B* and is then condensed in the tube by opening *A*. The tube is subsequently sealed off at *C*.

Analysis.—The sealed tube is heated at the temperature and for the time indicated in the Table in a multibarrel oven and then is placed in a tube II under an iron breaker and attached to the mass spectrometer inlet system by means of ground joints *L* and *K*.

After pumping out, the stopcock *A* is closed, the break-off tip smashed by operating the iron breaker with a magnet, and tube II is then cooled in liquid air. The carbon dioxide which is evolved when the tube is allowed to warm, is collected in another trap *T*, cooled in liquid air. The gas is purified by a further sublimation into the space behind the leak of the mass spectrometer. As a check on the purity of the gas the mass spectrum on either side of the

carbon dioxide peaks (44, 45, 46) is examined. If excessive peaks are observed when using this simple procedure, the samples may be purified more effectively as follows. The sealed tube is broken open in II, into which quinoline (0·5 ml.) has been added. The gas is condensed into bromine (0·5 ml.) in tube *E* by means of liquid air. Stopcock *D* is again closed, and the bromine is allowed to warm to room temperature and then cooled again to −80°. The gas is condensed back into tube II by means of liquid air, and the mixture with quinoline allowed to warm to room temperature. After a few minutes the quinoline is cooled to −80°, and the purified carbon dioxide transferred to the mass-spectrometer sample line.

Tests of Applicability.—The applicability of the procedure to various compounds was tested by determining (*a*) the extent to which the composition of the carbon dioxide approaches its theoretical value (ignoring isotope effects), (*b*) the degree of exchange of the alcohol oxygen atoms. Dividing equation (4) (p. 157), obtained for each alcohol from the calibrating experiments, by $m_1 + m_2 + m_3$, we obtain :

$$(f_1m_1 + m_2 + f_3m_3)/(m_1 + m_2 + m_3) = m_2(n_H - n_L)/(n_2 - n_1)(m_1 + m_2 + m_3)$$

Now the left-hand term is a measure of the deviation from ideal conditions, *i.e.*, complete equilibrium and absence of isotope effects. In the Table, col. 4, are presented values for various alcohols of the quotient :

$$100m_2(n_H - n_L)/(n_2 - n_1)(m_1 + m_2 + m_3) \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

The extent of exchange of the alcohol oxygen may also be derived from equation (4). Assuming that the sulphuric acid reaches complete statistical isotopic equilibrium with water ($f_3 = 1$), we obtain the following expression for f_1 :

$$f_1 = [m_2(n_H - n_L)/m_1(n_2 - n_1)] - (m_2 + m_3)/m_1 \quad . \quad . \quad . \quad . \quad (8)$$

Values of f_1 for various alcohols, expressed as percentages, are given in col. 5.

Percentage of equilibrium attained by carbon dioxide and the extent of exchange of oxygen atoms of organic compounds.

Compound	Temp.	Time, hr.	% equilibrium value of CO_2 (eqn. 7)	% of exchange of alcohol oxygen (eqn. 8)
Ethyl alcohol	200°	3	99	90
n-Butyl alcohol	200	3	95	65
n-Octyl alcohol	200	3	94	60
n-Dodecyl alcohol	200	3	94	60
Benzyl alcohol	200	1	99	90
*neo*Pentyl alcohol	230	3	97	77
*iso*Propyl alcohol	170	3	100	100
sec.-Butyl alcohol	170	3	100	100
Diphenylmethanol	170	3	100	100
2 : 2-Dimethyl-1-phenylpropanol	170	3	100	100
*cyclo*Hexanol	170	3	100	100
1-Phenylethanol	170	3	100	100
tert.-Butyl alcohol	150	1	100	100
tert.-Pentyl alcohol	150	1	100	100
3-Methylpentan-3-ol	150	1	100	100
Triphenylmethanol	200	3	70	13
1 : 1 : 2-Triphenylethanol	180	3	100	100
Cholesterol	180	1	31	17
Glycerol	200	3	100	100
Mannitol	200	3	91	48
Phenol	200	3	0	0
Acetone	180	3	96	70
Pentane-2 : 4-dione	200	3	99	90
Di-*n*-butyl ether	200	1	0	0
n-Butyl acetate	200	1	0	0

Effect of Tube Size.—*tert.*-Butyl alcohol was analysed under identical conditions (150° and 1 hr.) in tubes of 4·5, 1·3, and 0·4 ml. volume. The percentage of equilibrium attained by the carbon dioxide in these experiments was 90, 99, and 100, respectively.

Effect of Second Heat Treatment.—*neo*Pentyl alcohol was analysed by treatment at 230° for 3 hr. Without a second heat treatment the carbon dioxide reached 76% equilibrium, while after a further heating at 160° for 1 hr. the value was 99%.

Effect of Ratio of Alcohol to Carbon Dioxide.—Changing the ratio of *n*-butyl alcohol to carbon dioxide by a factor of two (alcohol : CO_2 = 1 : 0·065 and 2 : 0·065, in mmole) under identical conditions had little effect on the percentage exchange of equilibrium (94 and 95%).

Effect of Quantity of Acid.—The quantity of acid was reduced in one experiment with *tert.*-butyl alcohol by a factor of 10 (from 0·02 to 0·002 mmole) without affecting the percentage exchange of equilibrium by more than 1% (99% to 98%).

THE ISOTOPE DEPARTMENT, THE WEIZMANN INSTITUTE OF SCIENCE,
REHOVOT, ISRAEL. [*Received, August 11th*, 1954.]

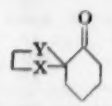
Syntheses using Monoketals of cyclo*Hexane*-1 : 2-*dione. Part I.* 2-*Oxo*-cyclo*hexane*-1-spiro-2′-1′ : 3′-*Dioxolan and the corresponding Oxathiolan and Dithiolan.*

By (MRS.) R. H. JAEGER and HERCHEL SMITH.

[Reprint Order No. 5692.]

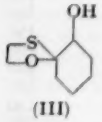
Treatment of *cyclo*hexane-1 : 2-dione with ethylene glycol, 2-mercaptoethanol, and ethane-1 : 2-dithiol by Salmi's procedure (*Ber.*, 1938, **71**, 1803) gave the mono- and di-ketals. 2-Hydroxy*cyclo*hexanone and ethylene glycol gave a monoketal. Observations are made on the structure of solid 2-hydroxy*cyclo*hexanone. Reductive desulphurization with Raney nickel of the hemithioketals (I*b*), (III), and (IV) is recorded. The mechanism of these reactions is discussed. With boiling Brady's reagent 2-ethyl-2-hydroxy-*cyclo*hexanone gave 2-ethyl*cyclo*hex-2-enone 2 : 4-dinitrophenylhydrazone.

THE present communication begins a series in which we shall describe the use of *cyclo*hexane-1 : 2-dione as a source for intermediates capable of forming the basis of rings C and D in D-homo-18-norsteroid systems. The compounds we require are certain 2-substituted *cyclo*hex-2-enones or their derivatives in which the carbonyl group is protected against anionoid reagents. It appeared that an obvious route to these would involve the protection of one of the carbonyl groups of *cyclo*hexane-1 : 2-dione whilst developing a side chain based on the other. The formation of cyclic ethylene ketals as a means of protecting carbonyl groups has recently found wide application in steroid syntheses (*inter al.*, Poos, Arth, Beyler, and Sarett, *J. Amer. Chem. Soc.*, 1953, **75**, 422; Wilds *et al.*, *ibid.*, p. 4878), and in 1952 we independently demonstrated the usefulness of the method in a synthesis of 5-acetyl-1 : 2 : 3 : 4 : 7 : 8 : 9 : 10-octahydro-10-methylnaphthalene-2-*spiro*-2′-1′ : 3′-dioxolan (Jaeger, Robinson, and Smith, unpublished work). Our experience in this field led us to investigate the same method with *cyclo*hexane-1 : 2-dione; accordingly we first investigated the preparation of 2-oxo*cyclo*hexane-1-*spiro*-2′-1′ : 3′-dioxolan (I*a*). The observation that a carbonyl group can be regenerated from an oxathiolan by treatment with Raney nickel

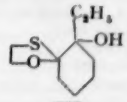


(I*a*); X = Y = O
(I*b*); X = O, Y = S
(I*c*); X = Y = S

(II*a*); X = Y = O
(II*b*); X = O, Y = S
(II*c*); X = Y = S



(III)



(IV)

(Romo, Rosenkrantz, and Djerassi, *J. Amer. Chem. Soc.*, 1951, **73**, 4961; Djerassi and Gorman, *ibid.*, 1953, **75**, 3704) prompted us to prepare also the corresponding oxathiolan (I*b*) and to treat it and the derived alcohols (III) and (IV) with Raney nickel. To complete the series we have also synthesized 2-oxo*cyclo*hexane-1-*spiro*-2′-1′ : 3′-dithiolan (I*c*).

Reaction of *cyclo*hexane-1 : 2-dione with one mol. of ethylene glycol in benzene in the presence of toluene-*p*-sulphonic acid by Salmi's method (*loc. cit.*) gave a mixture of the

monoketal (I*a*) and the diketal (II*a*), together with unchanged dione. The monoketal was obtained in low but reproducible yield (15—18%) and could only be satisfactorily separated from the diketal by chromatography on alumina. Reaction with an excess of ethylene glycol (2 mols.) under the same conditions gave only the diketal. Evidently ketal formation is easier with the monoketal than with the enolic *cyclo*hexane-1 : 2-dione. It is noteworthy that when the latter preparation was carried out with a much larger amount of catalyst there was also obtained a small quantity (*ca.* 2%) of a second diketal which is isomeric with the first and probably has the benzo-1 : 4-dioxan structure (V). This ketal could not be obtained by treatment of its isomer (II*a*) with toluene-*p*-sulphonic acid monohydrate under conditions of its formation from *cyclo*hexane-1 : 2-dione. The formulation (V) is in accord with the experimental conditions observed to produce the second diketal; for if formation of the ketal is discussed in terms of a conventional mechanism (Waters, " Physical Aspects of Organic Chemistry," Routledge and Kegan Paul Ltd., London, 1950, p. 336; Djerassi and Gorman, *loc. cit.*) the production of (V) from *cyclo*hexane-1 : 2-dione probably depends on the formation of an ion of the type (VI) and this would be expected to occur, although to a small extent only, under the influence of a high proton concentration.

The keto-ketal (I*a*) is hydrolysed by acid to *cyclo*hexane-1 : 2-dione comparatively slowly; this behaviour can be understood when it is realized that the strongly electron-attracting carbonyl group is bound directly to the carbon atom which must become cationic if hydrolysis is to proceed (cf. Ingold, " Structure and Mechanism in Organic Chemistry," G. Bell and Sons Ltd., London, 1953, p. 334). The reverse effect has been observed in the case of the acid hydrolysis of the acetals of pentaerythritol with formaldehyde, acetalde-

hyde, and acetone, increase in the number of electron-releasing substituents resulting in large increases in the reaction rate (Skrabal and Zlatewa, *Z. physikal. Chem.*, 1926, **122**, 349). The rates of hydrolysis of the ketals (II*a*) and (V) are extremely low; apart from purely steric effects, here again the co-ordination of a proton to a possible position of attack is inhibited by the inductive effect of an accumulation of electron-attracting *O*-alkyl substituents at the adjacent carbon atom.

Because of the low yield of (I*a*) obtained from *cyclo*hexane-1 : 2-dione we attempted to find an alternative method of preparation and investigated the reaction between 2-hydroxy*cyclo*hexanone and ethylene glycol, which proceeded in toluene in the presence of concentrated sulphuric acid to give 2-hydroxy*cyclo*hexane-1-*spiro*-2′-1′ : 3′-dioxolan whose structure follows from its identity with the lithium aluminium hydride reduction product of (I*a*). This could not be oxidized by Oppenauer's method or by treatment with the chromium trioxide–pyridine complex (Sarett *et al.*, *J. Amer. Chem. Soc.*, 1953, **75**, 1708). For the foregoing work a quantity of 2-hydroxy*cyclo*hexanone (adipoin) was prepared by alkaline hydrolysis of 2-chloro*cyclo*hexanone as recommended by Kötz *et al.* (*Annalen*, 1913, **400**, 62). The solid adipoin had properties similar to those described by Sheehan, O'Neill, and White (*J. Amer. Chem. Soc.*, 1950, **72**, 3376) who assigned to it a bimolecular lactolid structure on the basis of the infra-red spectrum and a Rast molecular-weight determination in camphor. Although our sample had been purified in a manner closely resembling that of Sheehan *et al.* we did not observe their value for the molecular weight. Rast determinations under a variety of conditions, in camphor or in *cyclo*pentadecanone (m. p. *ca.* 80°), gave a value of around 140, whilst cryoscopic measurements in water gave 107. Solid adipoin in pyridine at room temperature yielded a 3 : 5-dinitrobenzoate corresponding to monomeric 2-hydroxy*cyclo*hexanone; a solution obtained by boiling solid adipoin with chloroform for a short time had, after separation from the chiefly undissolved material, an

infra-red maximum of appreciable intensity at 5·84 μ. The melting point and insolubility of solid adipoin in common non-polar organic solvents favours a polymeric structure but the evidence we have presented indicates that disaggregation is so easy that any measurement involving dissolution or heat cannot reveal the true molecular weight. Supporting this view is our observation that when solid adipoin, previously showing no carbonyl band in the infra-red, is melted, a powerful carbonyl band appears, which disappears on crystallization and reappears on remelting. It seems likely, as suggested by Sheehan *et al.*, that the solid is mainly dimeric, but the presence of variable amounts of higher aggregates cannot be ruled out. This, and variations in the partial disaggregation on heating, may explain the different values obtained for the melting point of solid adipoin.

Reaction of *cyclo*hexane-1 : 2-dione with 2-mercaptoethanol by Salmi's method (*loc. cit.*) gave the monohemithioketal (I*b*) in about 40% yield, together with a mixture of diketals probably consisting mainly of the stereoisomers of (II*b*); one of these was obtained crystalline. With lithium aluminium hydride and ethylmagnesium bromide the ketonic derivative (I*b*) gave the alcohols (III) and (IV) respectively. These oxathiolans were each desulphurized under the same conditions with Raney nickel (Romo, Rosenkrantz, and Djerassi, *loc. cit.*); the ketone (I*b*) containing a powerfully electron-attracting group adjacent to the site of reaction gave none of the expected *cyclo*hexane-1 : 2-dione but a mixture consisting largely of 2-ethoxy*cyclo*hexanone and 2-ethoxy*cyclo*hexanol, with a little 2-hydroxy*cyclo*hexanone. The alcohol (III) containing a weaker electron-attracting group adjacent to the C–S bond gave *cyclo*hexane-1 : 2-diol and some 2-hydroxy*cyclo*hexanone, whilst the tertiary alcohol (IV) having adjacent electron-attracting and electron-repelling groups gave mainly 2-ethyl-2-hydroxy*cyclo*hexanone and only a trace of the corresponding diol. The products from the alcohols (III) and (IV) are consistent with a " normal " desulphurization accompanied by some reduction of a carbonyl group; that from (I*b*) apparently is anomalous.

Kenner, Lythgoe, and Todd (*J.*, 1948, 957), recalling that treatment of hydrazobenzene with Raney nickel in ethanol gave *N*-ethylaniline (Mozingo, Spencer, and Folkers, *J. Amer. Chem. Soc.*, 1944, **66**, 1859), suggested that desulphurization by this reagent involves attack by atomic hydrogen with the intermediate formation of free radicals, and this view has been supported by Hauptmann and Wladislaw (*J. Amer. Chem. Soc.*, 1950, **72**, 707, 711) and Bonner (*ibid.*, p. 1034; 1952, **74**, 1034). To account for the regeneration of a parent ketone from a hemithioketal Djerassi *et al.* (*loc. cit.*) invoked the intermediate formation of a 1 : 4-diradical, *e.g.*, $\cdot CR_2 \cdot O \cdot CH_2 \cdot CH_2 \cdot$, which stabilizes itself by the elimination of ethylene ($\longrightarrow R_2CO + C_2H_4$). Now almost any substituent in place of hydrogen stabilizes the amphoteric unpaired electron (references cited by Birch, *Quart. Reviews*, 1950, **4**, 72), and so if reductive desulphurization by Raney nickel is a free-radical process, it might be expected that alterations in the substitution at the position β to the sulphur atom should not affect the product. It may be, however, that the nature of the product is decided by the relative rates with which the diradical rearranges to a ketone or adds hydrogen to give an ethyl ether. In the compound (I*b*) the carbonyl group may so stabilize an adjacent unpaired electron that addition of hydrogen atoms to the diradical becomes the principal, but not the sole, reaction. Desulphurization by a heterolytic mechanism would give an ethyl ether and not a ketone, and the possibility that the powerful electron-attraction of the carbonyl group can call into play this type of mechanism (Hey, *Ann. Reports*, 1948, **45**, 139) in (I*b*) should also be noted.

When 2-ethyl-2-hydroxy*cyclo*hexanone was boiled for several minutes with Brady's reagent the 2 : 4-dinitrophenylhydrazone of 2-ethyl*cyclo*hex-2-enone was obtained. Similar dehydrations were observed with 2-hydroxy-2-methyl*cyclo*hexanone 2 : 4-dinitrophenylhydrazone and semicarbazone in hot mineral acid (Butz, Davis, and Gaddis, *J. Org. Chem.*, 1947, **12**, 122). This may be contrasted with the difficulty of dehydrating the α-ketol or its acetate by direct means (Butz *et al.*, *loc. cit.*). This type of reaction is probably quite general for 2-alkyl-2-hydroxyalkanones and is evidently related to the rapid dehydrobromination which occurs when α-bromo-ketones are treated with 2 : 4-dinitrophenylhydrazone in the presence of acid (Mattox and Kendall, *J. Amer. Chem. Soc.*, 1948, **70**, 882; Djerassi, *ibid.*, 1949, **71**, 1003).

Acid hydrolysis of the ketals (I*b*), (III), and (IV) was slow—in that order of increasing speed, in accordance with the expected electronic effects.

The dithioketal (I*c*) was best prepared from *cyclo*hexane-1 : 2-dione and ethane-1 : 2-dithiol by Salmi's method, the catalyst being toluene-*p*-sulphonic acid. Reaction at room temperature in the presence of zinc chloride and a dehydrating agent gave an unsatisfactory result.

Experimental

Light petroleum without further definition means the fraction of b. p. 60—80°. Infra-red spectra of solids were determined for Nujol mulls except where stated otherwise; approximate intensities of bands are given as: s = strong; m = medium; w = weak. Spectra were determined by Dr. F. B. Strauss with the technical assistance of Mr. F. Hastings.

2-*Oxo*cyclo*hexane*-1-spiro-2′-1′ : 3′-*dioxolan* (I*a*).—A solution of *cyclo*hexane-1 : 2-dione (15·8 g.) (Butz *et al.*, *loc. cit.*) and ethylene glycol (9 c.c.) in dry benzene (175 c.c.) was refluxed for 6 hr. with toluene-*p*-sulphonic acid (50 mg.), under a Dean–Stark water separator. Ether (150 c.c.) was added, unchanged diketone extracted with aqueous sodium hydroxide, and the organic layer washed, dried, and evaporated. The dark oil (14·5 g.) was adsorbed from light petroleum on alumina. Elution with light petroleum and light petroleum–benzene (1 : 1) gave cyclo*hexane*-1 : 2-*di*(spiro-2′-1′ : 3′-*dioxolan*) (II*a*) (6·5 g.) as a colourless oil, b. p. 130—133°/18 mm. [Found: C, 60·2; H, 7·9%; *M* (Rast), 190. $C_{10}H_{16}O_4$ requires C, 60·0; H, 8·0%; *M*, 200]; elution with benzene and benzene–ether (up to 1 : 4) yielded pure 2-*oxo*cyclo*hexane*-1-spiro-2′-1′ : 3′-*dioxolan* (3·5 g.) as a colourless oil, b. p. 115—116°/22 mm. (Found: C, 61·5; H, 7·8. $C_8H_{12}O_3$ requires C, 61·5; H, 7·7%). The infra-red spectrum had a band at 5·78 μ (s). Light absorption in MeOH: Max. = 295 mμ (ε = 38); compared with *cyclo*hexanone: Max. = 280 mμ (ε = 19). The 2 : 4-*dinitrophenylhydrazone*, prepared in pyridine (cf. Braude and Timmons, *J.*, 1953, 3131), separated from ethyl acetate–ethanol as orange-red prisms, m. p. 171° (Found: C, 49·9; H, 4·8; N, 16·7. $C_{14}H_{16}O_8N_4$ requires C, 50·0; H, 4·8; N, 16·7%).

The diketal (II*a*) was obtained in quantitative yield when *cyclo*hexane-1 : 2-dione was treated with ethylene glycol (2 mols.) under the above conditions. In one experiment *cyclo*hexane-1 : 2-dione (26·7 g.) and ethylene glycol (26 c.c.; 2 mols.) in dry benzene (260 c.c.) were refluxed as above with an unusually large amount of toluene-*p*-sulphonic acid (0·75 g.). Elimination of water was rapid and two non-ketonic products were obtained: (i) the normal diketal (II*a*) (33·6 g.) and (ii) a colourless oil (1 g.), b. p. 134—138°/18 mm., which crystallized from light petroleum (b. p. 40—60°) in prisms, m. p. 102—103°, to which the structure 1 : 2-1 : 2-*bisethylenedioxy*cyclo*hexane* (V) has been assigned [Found: C, 60·1; H, 8·0%; *M* (Rast), 223]. The infra-red spectrum of the liquid (II*a*) in CS_2 (17·4 mg./c.c.) had bands at 3·43s, 3·45s, 7·39m, 7·42m (infl.), 7·50m, 7·90m, 8·43s, 8·86s, 9·10s, 9·26s, 9·61s, 9·90m, 10·22s, 10·55s, 10·85w, 11·20w, 11·42w, 12·61w, and 13·07w μ. The infra-red spectrum of the solid (V) in CS_2 (17·4 mg./c.c.) had bands at 3·43s, 3·46s, 7·25w, 7·40s, 7·86s, 7·98s, 8·45s, 8·75s, 9·10s, 9·57s, 9·63s, 9·95s, 10·32s, 10·41s, 10·87s, 11·13s, 11·20s, 11·65w, 11·99s, 12·71w, and 13·20m μ.

The compounds (I*a*), (II*a*), and (V) were each refluxed with 50% acetic acid for 30 min. under nitrogen, and the products isolated by means of ether. Most of the starting materials (*ca.* 80—90%) were recovered. A small quantity of *cyclo*hexane-1 : 2-dione was identified by a ferric chloride test and by its characteristic odour; the amounts [*ca.* 20% from (I*a*) and *ca.* 5—10% from (II*a*) and (V)] were estimated from the infra-red spectra.

2-*Hydroxy*cyclo*hexane*-1-spiro-2′-1′ : 3′-*dioxolan*.—Reduction of the above *cyclo*hexanone-*spiro*dioxolan (2 g.) with lithium aluminium hydride in ether in the known manner gave 2-*hydroxy*cyclo*hexane*-1-spiro-2′-1′ : 3′-*dioxolan* as a colourless oil (1·5 g.), b. p. 115°/15 mm. (Found: C, 61·1; H, 9·1. $C_8H_{14}O_3$ requires C, 60·8; H, 8·9%). The 3 : 5-*dinitrobenzoate* separated from methanol as needles, m. p. 136—137° (Found: C, 51·3; H, 4·7; N, 7·8. $C_{15}H_{16}O_8N_2$ requires C, 51·2; H, 4·6; N, 8·0%).

2-*Hydroxy*cyclo*hexanone*.—This was prepared by Kötz's method (*loc. cit.*). It distilled at 98—100°/20 mm. and on recrystallization from acetone had m. p. 117—119° (softening at 100°) [Found: C, 63·2; H, 8·8; active H, 1·2%; *M* (Rast in camphor; Pyrex tube), 139, 144; *M* (Rast in *cyclo*pentadecanone), 141; *M* (cryoscopically in water), 107. Calc. for $C_6H_{10}O_2$: C, 63·2; H, 8·8; active H, 0·9%; *M*, 114]. The infra-red spectrum of the crystalline form exhibited a hydroxyl band at 3·0 μ and no carbonyl band in the 5·8 μ region. The freshly distilled oil showed a hydroxyl band at 2·99 μ and a carbonyl band at 5·86 μ. The latter disappeared on solidification but reappeared on remelting.

The 3 : 5-*dinitrobenzoate* crystallized from methanol in cream-coloured prisms, m. p. 146—148° [Found: C, 50·9; H, 4·0; N, 8·7%; *M* (Rast in camphor), 285. $C_{13}H_{12}O_7N_2$ requires C, 50·6; H, 3·9; N, 9·1%; *M*, 308]. The infra-red spectrum had strong bands of equal intensity at 5·76 μ and 5·84 μ.

The methyl ether of dimeric adipoin was prepared from the solid and methanolic hydrogen chloride (cf. Bergmann and Gierth, *Annalen*, 1926, **448**, 50) [Found: C, 65·7; H, 9·4; *M* (Rast in camphor), 224. Calc. for $C_{14}H_{24}O_4$: C, 65·5; H, 9·4%; *M*, 256].

Reaction of 2-*Hydroxy*cyclo*hexanone with Ethylene Glycol.*—2-Hydroxy*cyclo*hexanone (15 g.) and ethylene glycol (14·64 c.c.) were refluxed in toluene (250 c.c.) containing concentrated sulphuric acid (9 drops) for 3 hr., under a Dean–Stark water separator. The cooled mixture was washed with 2N-sodium hydroxide (2 × 100), and then water, and dried (Na_2SO_4). Distillation gave 2-hydroxy*cyclo*hexane-1-*spiro*-2′-1′ : 3′-dioxolan (9·0 g.), b. p. 62—64°/0·3 mm. (Found: C, 61·4; H, 9·0. Calc. for $C_8H_{14}O_3$: C, 60·8; H, 8·9%), probably containing some unchanged hydroxy*cyclo*hexanone which could not be entirely removed by fractionation. The infra-red spectrum shows bands at 2·88s, 5·85w μ and in the 8—10-μ region (s).

The 3 : 5-dinitrobenzoate, obtained in excellent yield, formed needles from ethanol, m. p. 136—137°, undepressed by the same derivative described above and possessing an identical infra-red spectrum (Found: C, 51·1; H, 4·5; N, 7·8%).

The hydroxy*cyclo*hexane*spiro*dioxolan was recovered unchanged after 6 hours' refluxing with aluminium *iso*propoxide and acetone in toluene; it also could not be oxidized by chromium trioxide–pyridine (Sarett *et al.*, *loc. cit.*).

2-*Oxo*cyclo*hexane*-1-spiro-2′-1′ : 3′-*oxathiolan* (I*b*).—A mixture of *cyclo*hexane-1 : 2-dione (20 g.), 2-mercaptoethanol (16 g.), toluene-*p*-sulphonic acid (100 mg.), and benzene (400 c.c.) was refluxed in an inert atmosphere for 6 hr. (Dean–Stark head) and worked up as described for the corresponding dioxolan. Fractionation of the crude product gave 2-*oxo*cyclo*hexane*-1-spiro-2′-1′ : 3′-*oxathiolan* (12·3 g.) as a colourless oil, b. p. 78—82°/0·3 mm. (Found: C, 56·0; H, 7·0; S, 18·4. $C_8H_{12}O_2S$ requires C, 55·8; H, 7·0; S, 18·6%). The infra-red spectrum had a strong band at 5·80 μ. The 2 : 4-*dinitrophenylhydrazone*, prepared with Brady's reagent, separated from ethyl acetate–ethanol as orange prisms, m. p. 178° (Found: C, 47·8; H, 4·4. $C_{14}H_{16}O_5N_4S$ requires C, 47·7; H, 4·5%). The fraction, b. p. 125—135°/0·3 mm., a colourless non-ketonic oil (8 g.), partly solidified. It was adsorbed from light petroleum on alumina and eluted with light petroleum. From the first eluate what is probably a stereoisomer of cyclo*hexane*-1 : 2-*di*(spiro-2′-1′ : 3′-*oxathiolan*) (II*b*) was obtained as a colourless, viscous oil, b. p. 130°/0·2 mm. (Found: C, 52·0; H, 6·9; S, 27·3. $C_{10}H_{16}O_2S_2$ requires C, 51·7; H, 6·9; S, 27·6%); further eluates contained an *isomer* which crystallized from light petroleum (b. p. 40—60°) as prisms, m. p. 135° (Found: C, 51·9; H, 6·9; S, 27·6%).

2-*Hydroxy*cyclo*hexane*-1-spiro-2′-1′ : 3′-*oxathiolan* (III).—The hemithioketal (I*b*) (1·3 g.) was refluxed with lithium aluminium hydride (0·85 g.) in ether (30 c.c.) for 30 min. "Celite 545" was added, followed by damp ether and water. Working up in the known manner gave 2-*hydroxy*cyclo*hexane*-1-spiro-2′-1′ : 3′-*oxathiolan* (1·1 g.), b. p. 80° (bath-temp.)/0·15 mm. (Found: C, 55·5; H, 7·9; S, 18·3. $C_8H_{14}O_2S$ requires C, 55·2; H, 8·05; S, 18·4%). The 3 : 5-*dinitrobenzoate* crystallized from ethanol in off-white needles, m. p. 144° (Found: C, 47·8; H, 4·4; N, 7·9; S, 8·7. $C_{14}H_{16}O_7N_2S$ requires C, 47·2; H, 4·5; N, 7·9; S, 9·0%).

2-*Ethyl*-2-*hydroxy*cyclo*hexane*-1-spiro-2′-1′ : 3′-*oxathiolan* (IV).—An ethereal solution of (I*b*) (3·5 g.) was added gradually with stirring to an ice-cold one of ethylmagnesium bromide (from 2·1 g. of magnesium and 10·6 g. of ethyl bromide in nitrogen). After 12 hr. at room temperature the mixture was refluxed for 7 hr., then decomposed with aqueous ammonium chloride, and the product was isolated with ether. The *spiran* distilled as a pale yellow, mobile oil (3·4 g.), b. p. 100°/0·1 mm. (Found: C, 59·6; H, 8·9; S, 15·9. $C_{10}H_{18}O_2S$ requires C, 59·5; H, 8·9; S, 15·8%). The infra-red spectrum had bands at 2·88m, 8·7s, and 9·35s μ.

Desulphurization of the Hemithioketals (I*b*), (III), *and* (IV) (cf. Romo, Rosenkrantz, and Djerassi, *loc. cit.*).—(i) A solution of the spiran (I*b*) (1 g.) in acetone (200 c.c.) was refluxed for 3 hr. with W-2 Raney nickel (10 g.), the catalyst filtered off, and the solvent evaporated. The pleasant-smelling, colourless oil (0·6 g.), b. p. 90°/24 mm., which gave no ferric chloride reaction (absence of *cyclo*hexane-1 : 2-dione), was a mixture of, chiefly, 2-ethoxy*cyclo*hexanone, 2-ethoxy-*cyclo*hexanol, and very little 2-hydroxy*cyclo*hexanone (Found: C, 67·2; H, 10·4; OEt, 30·2. Calc. for $C_8H_{14}O_2$: C, 67·6; H, 9·9; OEt, 31·6. Calc. for $C_8H_{16}O_2$: C, 66·7; H, 11·1; OEt, 31·2%). The infra-red spectrum had bands at 2·95, 5·82, and 9·05 μ. Boiling this mixture (0·15 g.) for 3 min. with Brady's reagent gave *cyclo*hexane-1 : 2-dione bis-2 : 4-dinitrophenylhydrazone (*ca.* 50 mg.) which crystallized from ethyl acetate in bright red prisms, m. p. 233—235°

(decomp.) (cf. Campbell and McCall, *J.*, 1950, 2870) (Found : C, 46·1; H, 3·6; N, 24·0. Calc. for $C_{18}H_{16}O_8N_8$: C, 45·9; H, 3·4; N, 23·8%). Light absorption in $CHCl_3$: Max. = 350 (ε 32,000) and 395 mμ (ε 25,000).

Another portion of the above mixture (0·15 g.) was boiled for 3 min. with pyridine (1 c.c.) and 2 : 4-dinitrophenylhydrazone (0·25 g.) (cf. Braude and Timmons, *loc. cit.*); benzene (20 c.c.) was added and the solution adsorbed on alumina. Elution with benzene gave 2-*ethoxy*cyclo*hexanone* 2 : 4-*dinitrophenylhydrazone*, which crystallized from benzene–light petroleum as yellow needles, m. p. 130° (Found : C, 52·3; H, 5·5; N, 17·2. $C_{14}H_{18}O_5N_4$ requires C, 52·2; H, 5·6; N, 17·4%). Elution with benzene–ethyl acetate (9 : 1) yielded a second 2 : 4-*dinitrophenylhydrazone* of 2-ethoxy*cyclo*hexanone, which separated from light petroleum as orange needles, m. p. 116°, depressed on admixture with the higher-melting derivative (Found : C, 52·2; H, 5·7; N, 17·1%). These two derivatives are probably *syn*- and *anti*-forms.

A third portion of the desulphurization product yielded 2-*ethoxy*cyclo*hexyl* 3 : 5-*dinitrobenzoate* which, after chromatography on "Florex," crystallized from light petroleum (b. p. 40—60°) in almost colourless prisms, m. p. 77—78° (Found : C, 53·8; H, 5·4; N, 8·5. $C_{15}H_{16}O_7N_2$ requires C, 53·3; H, 5·3; N, 8·3%).

(ii) The alcohol (III) (0·45 g.) was treated with Raney nickel as described above. The resultant liquid (0·3 g.), b. p. 120°/20 mm., consisted of *cyclo*hexane-1 : 2-diol accompanied by a little 2-hydroxy*cyclo*hexanone (Found : C, 62·5; H, 9·9. Calc. for $C_6H_{12}O_2$: C, 62·1; H, 10·0%). The infra-red spectrum had bands at 3·0s and 5·85w μ. *cyclo*Hexane-1 : 2-diol bis-3 : 5-dinitrobenzoate, crystallized from ethanol, had m. p. 177° (Wilson and Read, *J.*, 1935, 1269, give m. p. 179° for the derivative from the *trans*- and m. p. 169° for that of the *cis*-diol) (Found : C, 47·7; H, 3·4; N, 10·8. Calc. for $C_{20}H_{16}O_{12}N_4$: C, 47·7; H, 3·2; N, 11·1%). Boiling a sample of the desulphurization product with Brady's reagent yielded a small quantity of 2-hydroxy*cyclo*hexanone 2 : 4-dinitrophenylosazone, m. p. 234—235° (decomp.), undepressed on admixture with a previously prepared specimen.

(iii) Treatment of the alcohol (IV) (1 g.) with Raney nickel as above gave 2-*ethyl*-2-*hydroxy*cyclo*hexanone* (0·65 g.), b. p. 115—120°/20 mm. (Found : C, 67·2; H, 10·1. $C_8H_{14}O_2$ requires C, 67·5; H, 9·9%). The infra-red spectrum showed bands at 2·93s and 5·85s μ. This α-ketol, on 5 minutes' boiling with Brady's reagent, yielded 2-*ethyl*cyclo*hex*-2-*enone* 2 : 4-*dinitrophenylhydrazone*, dark red elongated prisms (from ethyl acetate), m. p. 229—231° (Found : C, 55·3; H, 5·4; N, 18·4. $C_{14}H_{16}O_4N_4$ requires C, 55·3; H, 5·3; N, 18·4%). Light absorption in chloroform : Max. = 385 mμ (ε = 25,600). The 3 : 5-*dinitrobenzoate* of the α-ketol crystallized, after chromatography on "Florex" and elution with light petroleum–benzene (3 : 1), in cream-coloured prisms (from methanol), m. p. 127° (Found : C, 53·8; H, 4·9; N, 8·4. $C_{15}H_{14}O_7N_2$ requires C, 53·6; H, 4·8; N, 8·3%).

Acid Hydrolysis of the Hemithioketals (I*b*), (III), *and* (IV).—The compounds were refluxed with aqueous-ethanolic hydrogen chloride for 3—5 hr. in nitrogen (cf. Djerassi, *J. Amer. Chem. Soc.*, 1953, **75**, 3704). In each case most of the starting material was recovered. The spiran (I*b*) yielded less than 5% of *cyclo*hexane-1 : 2-dione, identified by ferric chloride reaction and estimated from the infra-red spectrum. The spiran (III) gave 5—10% and (IV) *ca.* 15—20% of the dione, which was converted into the bis-2 : 4-dinitrophenylhydrazone, m. p. 235°.

2-*Oxo*cyclo*hexane*-1-spiro-2′-1′ : 3′-*dithiolan* (I*c*).—*cyclo*Hexane-1 : 2-dione (3·6 g.) was refluxed (Dean–Stark water separator) for 6 hr. under nitrogen with ethanedithiol (3·3 g.), dry benzene (80 c.c.), and toluene-*p*-sulphonic acid (20 mg.), and the mixture worked up as described for (I*b*). After fractionation the distillate, b. p. 94°/0·2 mm., consisting of 2-*oxo*cyclo*hexane*-1-spiro-2′-1′ : 3′-*dithiolan*, crystallized from light petroleum in colourless needles (2·2 g.), m. p. 57·5° (Found : C, 51·3; H, 6·5; S, 33·8. $C_8H_{12}OS_2$ requires C, 51·0; H, 6·4; S, 34·0%). The infra-red spectrum had a strong band at 5·87 μ. The fraction, b. p. 155—165°/0·2 mm. yielded cyclo*hexane*-1 : 2-*di*(spiro-2′-1′ : 3′-*dithiolan*) (II*c*) which separated from ethyl acetate as colourless prisms, m. p. 156° (Found : C, 45·7; H, 5·9; S, 48·1. $C_{10}H_{16}S_4$ requires C, 45·5; H, 6·1; S, 48·5%).

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2′-Hydroxy- and 2′-Methoxy-flavanones.

By T. H. Simpson and W. B. Whalley.

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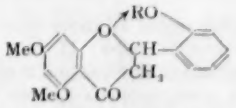
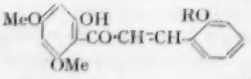
The compounds obtained by Narasimhachari, Rajagopalan, and Seshadri (*Proc. Indian Acad. Sci.*, 1952, **36**, *A*, 231) from the interaction of *o*-hydroxyacetophenones with *o*-hydroxy- and *o*-methoxy-benzaldehydes, and designated as 2′-hydroxyflavanones have been shown to be the respective unchanged parent *o*-hydroxyacetophenones. The preparation of various chalkones and related derivatives is described.

The isolation from *Citrus limon ponderosa* of a glycoside, citronin, which upon hydrolysis furnished the aglucone, citronetin, has been described by Yamamoto and Oshima (*J. Agric. Chem. Soc., Japan*, 1931, **7**, 312). Degradative evidence, especially the isolation of *o*-methoxycinnamic acid and phloroglucinol rhamnoglucoside from citronin by alkali fission, led them to formulate citronetin as 5 : 7-dihydroxy-2′-methoxyflavanone. This flavanone was synthesised by Shinoda and Sato (*J. Pharm. Soc. Japan*, 1931, **51**, 576) by the Friedel–Crafts condensation of phloroglucinol and *o*-methoxycinnamoyl chloride. However, as the melting point of natural citronetin (204°) was not in good accord with that of 5 : 7-dihydroxy-2′-methoxyflavanone (224°), Narasimhachari, Rajagopalan, and Seshadri (*Proc. Indian Acad. Sci.*, 1952, **36**, *A*, 231) re-investigated the synthesis of this and of 2′-hydroxy- and 2′-methoxy-flavanones.



(I)



(II)

From interaction of salicylaldehyde with 2-hydroxy-4 : 6-dimethoxyacetophenone in the presence of alkali the Indian authors (*loc. cit.*) isolated a product, m. p. 85—86°, which exhibited a blue colour with concentrated nitric acid, a violet ferric reaction in alcohol, a red colour with magnesium and hydrochloric acid, gave a negative boric acid test (Wilson, *J. Amer. Chem. Soc.*, 1939, **61**, 2303), and was only sparingly soluble in aqueous sodium hydroxide. An identical product was obtained from the same two components in the presence of hydrogen chloride (Russell, *J.*, 1934, 218). Furthermore, this compound was also obtained by the alkaline condensation of 2-hydroxy-4 : 6-dimethoxyacetophenone with *o*-methoxybenzaldehyde. This product, m. p. 85—86°, was formulated as 2′-hydroxy-5 : 7-dimethoxyflavanone (I; R = H). Its analysis was in agreement with the empirical formula $C_{17}H_{16}O_5,1{\cdot}5H_2O$, though it was stated that sublimation under reduced pressure did not change the m. p. or remove the water of crystallisation. If this compound is correctly formulated, its formation from *o*-methoxybenzaldehyde must involve a remarkably easy demethylation of the 2′-methoxy-group in 2′-methoxyflavanones. Seshadri *et al.* (*loc. cit.*) recognised this difficulty but circumvented it by assuming a new type of hydrogen bonding between the ether oxygen atom of the pyrone ring and the 2′-hydroxyl group (as in I; R = H), reminiscent of that existing between the pyrone carbonyl and the 5-hydroxyl group. This " new effect of hydrogen-bond formation " was also invoked to explain the ferric reaction of the compound, the alleged resistance to complete methylation and the inertness to oxidation with iodine and potassium acetate (Narashimhachari, Rajagopalan, and Seshadri, *Proc. Indian Acad. Sci.*, 1953, **37**, *A*, 620) and with hydrogen peroxide (*idem*, *ibid.*, p. 705).

Finally the cyclisation of 2′-hydroxy-2 : 4′ : 6′-trimethoxychalkone (II; R = Me) with boiling acid was reported to furnish (I; R = H) with the simultaneous demethylation of the 2′-methoxyl group of the resulting flavanone, though the acid-catalysed cyclisations of 2′-hydroxy-2 : 4′ : 6′-trimethoxy- (Bargellini and Peratoner, *Gazzetta*, 1919, **49**, 68), 2′-hydroxy-2 : 3′ : 4′-trimethoxy- (Cohen and von Kostanecki, *Ber.*, 1904, **37**, 2629), and

2'-hydroxy-2 : 4 : 4'-trimethoxy-chalkone (von Kostanecki, Lampe, and Triulzi, *Ber.*, 1906, **39**, 93) to the respective 2'-methoxyflavanones have previously been reported to be normal.

Such *a priori* unacceptable features prompted us to reinvestigate this problem. We now consider that the compound formulated as 2'-hydroxy-5 : 7-dimethoxyflavanone is actually unchanged 2-hydroxy-4 : 6-dimethoxyacetophenone. In numerous attempts to repeat both the acid- and the alkali-catalysed condensations of this ketone with salicylaldehyde and *o*-methoxybenzaldehyde (by the methods of Seshadri *et al.*, *locc. cit.*) the only solid product isolated by us was the parent ketone identified by analysis, melting point (86°), mixed melting point, and by paper chromatography. Furthermore, 2-hydroxy-4 : 6-dimethoxyacetophenone has the melting point and gives all the colour reactions (with the exception of the magnesium–hydrochloric acid test) ascribed to the flavanone (I; R = H).

In agreement with Bargellini and Peratoner (*loc. cit.*) we have found that the acid-catalysed cyclisation of 2'-hydroxy-2 : 4' : 6'-trimethoxychalkone (II; R = Me) proceeds normally to produce 5 : 7 : 2'-trimethoxyflavanone (I; R = Me), m. p. 128°, exhibiting all the expected properties and not being demethylated during cyclisation. In addition, the acid-catalysed cyclisation of 2 : 2'-dihydroxy-4' : 6'-dimethoxychalkone (II; R = H) furnished 2'-hydroxy-5 : 7-dimethoxyflavanone (I; R = H), m. p. 196°, which is instantly soluble in cold dilute alkali, is *devoid* of a ferric reaction, and is rapidly methylated to 5 : 7 : 2'-trimethoxyflavanone (I; R = Me).

The melting point of (I; R = Me) is in close agreement with that recorded by Yamamoto and Oshima (*loc. cit.*) for citronetin dimethyl ether (125°), formulated as 5 : 7 : 2'-trimethoxyflavanone. In consequence, we believe that the structure of citronetin, while still requiring final verification, is in all probability correct.

Repetition of the remaining "2'-hydroxyflavanone" preparations described by Seshadri *et al.* (*locc. cit.*), has clearly shown that these "2'-hydroxyflavanones" also are the appropriate *o*-hydroxyacetophenones. This conclusion is adequately substantiated by a comparison of the melting points, the colour reactions, the inertness towards oxidation by hydrogen peroxide, and the majority of analyses ascribed to these supposed flavanones and their derivatives, with those of the relevant ketones. Moreover, by standard methods, we have prepared the chalkones isomeric with Seshadri's "flavanones" and find that these styryl ketones are oxidised normally to the corresponding 3-hydroxyflavones and exhibit no abnormal properties.

Although we consider that some hydrogen bonding between the pyrone oxygen and the 2'-hydroxyl group of flavanones is likely (cf. Gallagher, Hughes, O'Donnell, Philbin, and Wheeler, *J.*, 1953, 3770), we conclude that the system does not possess the properties attributed to it by the Indian authors.

[*Note Added in Proof, November 17th*, 1954.—Our attention has been directed to a discrepancy in the literature of 2-methoxyflavones. 3-Hydroxy-7 : 2'-dimethoxyflavone, prepared by hydrolysis of the *iso*nitrosoflavanone is described by Kostanecki and Szlagier (*Ber.*, 1904, **37**, 4155) as forming tablets, m. p. 203° (acetate, m. p. 138—139°). Seshadri *et al.* (*Proc. Indian Acad. Sci.*, 1953, **37**, 705) claim to have prepared this compound by oxidation of the chalkone with alkaline hydrogen peroxide, but give m. p. 158—160°. We have now repeated the peroxide oxidation of 2'-hydroxy-2 : 4'-dimethoxychalkone and find, in agreement with Kostanecki and Szlagier (*loc. cit.*), that the flavonol has m. p. 204—205° (acetate, m. p. 138—139°)].

Experimental

5 : 7 : 2'-*Trimethoxyflavanone* (I; R = Me).—(*a*) A solution of sodium hydroxide (10 g.) in water (10 ml.) and alcohol (20 ml.) containing 2-hydroxy-4 : 6-dimethoxyacetophenone (5 g.) and salicylaldehyde (8 g.) was refluxed for 30 min., in an atmosphere of nitrogen. The crude product, isolated by acidification of the cold solution, was washed with light petroleum (b. p. 60—80°) and purified from alcohol to furnish 2 : 2'-*dihydroxy*-4' : 6'-*dimethoxychalkone* (6·5 g.) in yellow needles, m. p. 171°, having an intense red ferric reaction in alcohol (Found : C, 67·8; H, 5·1. $C_{17}H_{16}O_5$ requires C, 68·0; H, 5·4%). A solution of this chalkone (4 g.) in alcohol (320 ml.) and 2N-sulphuric acid (80 ml.) was refluxed for 48 hr., and the bulk of the alcohol

was then removed under reduced pressure. After dilution with water (100 ml.) the red, sticky precipitate was separated, and the solution of this in methanol deposited *2'-hydroxy-5 : 7-dimethoxyflavanone* (I; R = H) in almost colourless prisms (0·3 g.), m. p. 196°, instantly soluble in cold 2N-sodium hydroxide and devoid of a ferric reaction in alcohol [Found : C, 67·8; H, 5·3; OMe, 20·6. $C_{15}H_{10}O_3(OMe)_2$ requires C, 68·0; H, 5·4; OMe, 20·7%].

Ether extraction of the aqueous solution furnished more (0·2 g.) of this flavanone which was methylated quantitatively during 30 min. by methyl iodide or methyl sulphate–acetone–potassium carbonate to 5 : 7 : 2'-trimethoxyflavanone, identical with a specimen prepared by route (*b*).

(*b*) A solution of 2'-hydroxy-2 : 4' : 6'-trimethoxychalkone (1 g.) (prepared from the condensation of 2-hydroxy-4 : 6-dimethoxyacetophenone with *o*-methoxybenzaldehyde or by methylation with methyl sulphate–acetone–potassium carbonate of 2 : 2'-dihydroxy-4' : 6'-dimethoxychalkone) in 4% aqueous alcoholic sulphuric acid (100 ml.) was refluxed for 24 hr. (*cf.* Seshadri *et al., loc. cit.*). After unchanged chalkone (0·3 g.) had been filtered off from the cooled mixture, the solution was evaporated under reduced pressure to *ca.* 25 ml., and water (100 ml.) added to the residue. Purification of the resultant precipitate from methanol furnished (i) unchanged chalkone (0·1 g.), and (ii) 5 : 7 : 2'-trimethoxyflavanone (0·5 g.) in plates, m. p. 128°, having a negative ferric reaction in alcohol [Found : C, 68·7; H, 6·0; OMe, 29·6. Calc. for $C_{15}H_9O_3(OMe)_3$: C, 68·8; H, 5·8; OMe, 29·6%)]. Bargellini and Peratoner (*loc. cit.*) record m. p. 125°. The mixed m. p. with 2 : 2' : 4' : 6'-tetramethoxychalkone (m. p. 125°) was depressed to *ca.* 100°.

3 : 5 : 7 : 2'-*Tetrahydroxyflavone* (*Datiscetin*).—When hydrogen peroxide (100-vol.; 7·5 ml.) was added gradually to a solution of 2 : 2'-dihydroxy-4' : 6'-dimethoxychalkone (0·5 g.) in 30% sodium hydroxide (10 ml.), and the mixture acidified 30 min. later, the precipitated *3 : 2'-dihydroxy-5 : 7-dimethoxyflavone* separated from methanol in cream needles (0·25 g.), m. p. 216—218°, having a green ferric reaction in alcohol [Found : C, 65·1; H, 4·5; OMe, 19·6. $C_{15}H_6O_4(OMe)_2$ requires C, 65·0; H, 4·5; OMe, 19·7%]; the *diacetate* separated from alcohol in needles, m. p. 156° (Found : C, 63·3; H, 4·7. $C_{21}H_{18}O_8$ requires C, 63·3; H, 4·6%).

Demethylation of the foregoing flavone (1 g.) with a mixture of hydriodic acid (*d* 1·7; 2·5 ml.) and acetic acid (25 ml.) on the steam-bath during 1½ hr. furnished *3 : 5 : 2'-trihydroxy-7-methoxyflavone* in prisms (0·27 g.) (from alcohol), m. p. 240°, having a green ferric reaction in alcohol [Found : C, 64·0; H, 3·9; OMe, 10·7. $C_{15}H_9O_5(OMe)$ requires C, 64·0; H, 4·0; OMe, 10·3%].

Demethylation of 3 : 2'-dihydroxy-5 : 7-dimethoxyflavone (0·2 g.) with boiling hydriodic acid (*d* 1·7; 3 ml.)–acetic acid (from 1 ml. of anhydride) during 2 hr. furnished 3 : 5 : 7 : 2'-tetrahydroxyflavone which separated from aqueous acetic acid in pale yellow needles (0·095 g.), m. p. 277—278° undepressed on admixture with authentic datiscetin. The same product was obtained from 3 : 5 : 2'-trihydroxy-7-methoxyflavone or with aluminium chloride in benzene as the demethylating agent.

2 : 2'-*Dihydroxy-6'-methoxychalkone*.—The condensation of 2-hydroxy-6-methoxyacetophenone (5 g.) with salicylaldehyde (10 g.) by the method previously described furnished the *chalkone* in orange needles (7 g.), m. p. 141° (from aqueous alcohol), having an intense brown ferric reaction in this solvent [Found : C, 71·4; H, 5·3; OMe, 11·8. $C_{15}H_{11}O_3(OMe)$ requires C, 71·1; H, 5·2; OMe, 11·5%].

Chalkones derived from Paeonol.—A solution of sodium hydroxide (10 g.) in the minimum quantity of water was added to a solution of paeonol (6 g.) and *o*-methoxybenzaldehyde (10 g.) in alcohol (40 ml.). Next day, after the addition of excess of ether, the precipitated sodium salts were collected and dissolved in aqueous acetic acid, and the resultant solid purified from alcohol to furnish 2'-hydroxy-2 : 4'-dimethoxychalkone (9·5 g.) in yellow prisms, m. p. 92° (Kostanecki and Szlagier, *Ber.*, 1904, **37**, 4155, give m. p. 94°), with an intense brown ferric reaction in this solvent (Found : C, 72·1; H, 5·8. Calc. for $C_{17}H_{16}O_4$: C, 71·8; H, 5·7%). Seshadri *et al.* (*Proc. Indian Acad. Sci.*, 1953, **37**, *A*, 707) obtained this compound as a semi-solid.

The condensation of paeonol (2 g.) with salicylaldehyde (4 g.) in the usual manner furnished *2 : 2'-dihydroxy-4'-methoxychalkone* as yellow prisms (from aqueous alcohol) (2·2 g.), m. p. 176—178° (decomp.), having a red-brown ferric reaction in alcohol [Found : C, 71·0; H, 5·2; OMe, 11·9. $C_{15}H_{11}O_3(OMe)$ requires C, 71·1; H, 5·2; OMe, 11·5%].

Methylation of this chalkone, with methyl sulphate–aqueous sodium hydroxide at room temperature, furnished an almost quantitative yield of 2'-hydroxy-2 : 4'-dimethoxychalkone, m. p. 92°, identical with the previously prepared specimen.

The benzylation, during 5 hr., of 2 : 2'-dihydroxy-4'-methoxychalkone with benzyl bromide

in boiling acetone containing potassium carbonate furnished *2-benzyloxy-2′-hydroxy-4′-methoxychalkone* (50%), as yellow prisms (from alcohol), m. p. 117° (Found : C, 76·9; H, 5·5. $C_{23}H_{20}O_4$ requires C, 76·7; H, 5·6%), identical with the product (8 g.) obtained by the condensation of paeonol (8 g.) with *o*-benzyloxybenzaldehyde (14 g.) under the usual conditions.

3 : 7 : 2′-*Trihydroxyflavone.*—(*a*) The oxidation, during 30 min., of a solution of 2 : 2′-dihydroxy-4′-methoxychalkone (0·5 g.) in 30% sodium hydroxide (10 ml.) with hydrogen peroxide (100-vol.; 7·5 ml.) furnished 3 : 2′-*dihydroxy-7-methoxyflavone* in needles (from alcohol) (0·16 g.), m. p. 176—178°, with an intense green-brown ferric reaction in alcohol [Found : C, 67·8; H, 4·5; OMe, 10·9. $C_{15}H_9O_4$(OMe) requires C, 67·6; H, 4·3; OMe, 10·9%]. The *diacetate* formed prisms (from alcohol), m. p. 180° (Found : C, 65·0; H, 4·2. $C_{20}H_{16}O_7$ requires C, 65·2; H, 4·4%). Demethylation of the foregoing flavone (1 g.) during 1 hr. in boiling hydriodic acid (*d* 1·7; 10 ml.)–acetic acid (from 5 ml. of anhydride) furnished 3 : 7 : 2′-trihydroxyflavone, m. p. 272—273°, identical with an authentic specimen.

(*b*) The addition, during 20 min., of hydrogen peroxide (100-vol.; 20 ml.) to the well-cooled slurry from aqueous sodium hydroxide (8·5 g.) in the minimum of water and 2-benzyloxy-2′-hydroxy-4′-methoxychalkone (1 g.) in alcohol (50 ml.) furnished 2′-*benzyloxy-3-hydroxy-7-methoxyflavone* in prisms (acetic acid) (0·42 g.), m. p. 176°, having an intense dark green ferric reaction in alcohol (Found : C, 74·1; H, 4·8. $C_{23}H_{18}O_5$ requires C, 73·8; H, 4·9%). The *diacetate* formed plates, m. p. 148°, from alcohol (Found : C, 71·7; H, 4·7. $C_{23}H_{20}O_6$ requires C, 72·1; H, 4·8%).

Debenzylation of 2′-benzyloxy-3-hydroxy-7-methoxyflavone (1·5 g.) in acetic acid (25 ml.) containing concentrated hydrochloric acid (18 ml.) on the steam-bath during 1 hr. furnished 3 : 2′-dihydroxy-7-methoxyflavone (0·85 g.) identical with the previously prepared specimen.

3 : 2′-*Dihydroxy- and* 3-*Hydroxy-2′-methoxy-flavone.*—The oxidation with hydrogen peroxide of 2 : 2′-dihydroxychalkone (Geissmann and Clinton, *J. Amer. Chem. Soc.*, **1946**, **68**, 698) (0·5 g.) furnished 3 : 2′-*dihydroxyflavone* in yellow plates (0·12 g.), m. p. 209°, from alcohol (Found : C, 71·0; H, 4·1. $C_{15}H_{10}O_4$ requires C, 70·9; H, 4·0%); the *diacetate* formed needles, m. p. 124°, from alcohol (Found : C, 67·4; H, 4·4. $C_{19}H_{14}O_6$ requires C, 67·5; H, 4·2%).

Similarly 2′-hydroxy-2-methoxychalkone (Tambor and Guber, *Helv. Chim. Acta*, **1919**, **2**, 108) (1 g.) gave 3-*hydroxy-2′-methoxyflavone* in pale yellow prisms (0·35 g.), m. p. 215° [Found : C, 71·6; H, 4·5; OMe, 11·3. $C_{15}H_9O_3$(OMe) requires C, 71·6; H, 4·5; OMe, 11·6%]. The *diacetate* crystallised from alcohol in plates, m. p. 155° (Found : C, 69·9; H, 4·6. $C_{19}H_{14}O_5$ requires C, 69·7; H, 4·6%). Demethylation of this flavone (1 g.) with boiling hydriodic acid (*d* 1·7; 15 ml.) and acetic acid (from 5 ml. of anhydride) during 30 min. gave 3 : 2′-dihydroxyflavone (0·5 g.), identical with the previously prepared specimen.

The authors are indebted to Dr. G. H. Whitham for the synthesis of several of the compounds. The work described in this paper was carried out as part of the programme of the Food Investigation Organisation of the Department of Scientific and Industrial Research.

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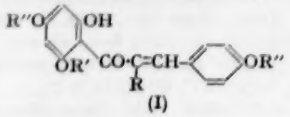
Anthoxanthins. Part II. Derivatives of Katuranin and Kaempferol.*

By (Miss) J. M. Guider, T. H. Simpson, and (in part) D. B. Thomas.

[Reprint Order No. 5723.]

The synthesis of the 7-methyl, 5 : 7- and 7 : 4′-dimethyl, and 5 : 7 : 4′-trimethyl ethers of katuranin (II; R = OH, R′ = R″ = R‴ = H) is described. Bismuth acetate smoothly oxidised these compounds to the corresponding derivatives of kaempferol (III; R = R′ = R″ = R‴ = H) which were also prepared by standard methods.

In Part I * it was shown that flavone hydroxyl groups in flavones are not all equally reactive and that by suitable choice of conditions some selectivity in methylation can be achieved. Since the differences between the methylation rates of 7- and 4′-hydroxyl groups and between those of 3- and 4′-hydroxyl groups are small, satisfactory monomethylation of 7 : 4′- and 3 : 4′-dihydroxyflavones proved difficult. It was considered that these partial methylations might more readily be accomplished if the pyrone ring were reduced (Seshadri, *Ann. Reviews Biochem.*, 1951, **20**, 487). The present investigation of 3-hydroxyflavanones as intermediates in the synthesis of partially methylated flavonols was undertaken as a preliminary to syntheses of naturally occurring flavone glycosides.



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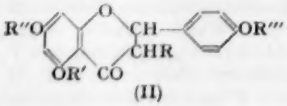

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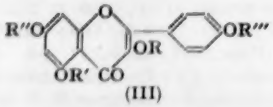

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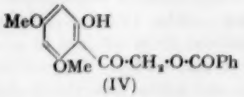

(IV)

Oxidation of **4** : 2′-dihydroxy-4′ : 6′-dimethoxychalkone (I; R = R‴ = H, R′ = R″ = Me) with alkaline hydrogen peroxide (Reichel and Steudel, *Annalen*, **1942**, **553**, 83) gave **3** : 4′-dihydroxy-**5** : 7-dimethoxyflavanone (II; R = OH, R′ = R″ = Me, R‴ = H) which had no ferric reaction in ethanol and with zinc and hydrochloric acid gave the intense cherry red colour characteristic of 3-hydroxyflavanones (Pew, *J. Amer. Chem. Soc.*, 1948, **70**, 3031). With methyl sulphate and aqueous alkali, the 3-hydroxyflavanone yielded its 4′-methyl ether, previously obtained by Goel, Narasimhachari, and Seshadri (*Proc. Indian Acad. Sci.*, **1954**, **39**, *A*, 254) by methylation of katuranin (II; R = OH, R′ = R″ = R‴ = H). This structure has also been ascribed by Kimuru (*J. Pharm. Soc. Japan*, 1938, **58**, 415; *Chem. Abs.*, 1938, **32**, 6649) to the product of acid-catalysed cyclisation of 2′-hydroxy-α : **4** : 4′ : 6′-tetramethoxychalkone (I; R = OMe, R′ = R″ = R‴ = Me); this product, m. p. 158—159°, is probably a different racemate from that described by Seshadri *et al.* (*loc. cit.*) and the present authors.

3-Hydroxyflavanones have been converted into the corresponding flavonols (III) by alkaline hydrogen peroxide (Reichel and Steudel, *loc. cit.*), by aerial oxidation in acid (Pew, *loc. cit.*) or alkaline (Reichel and Steudel, *loc. cit.*) solution and by catalysed hydrogen transfer (Kotake and Kubota, *Annalen*, 1940, **544**, 253). In our hands, however, the yields obtained by these procedures were variable and low. This transformation may be envisaged as a two-stage process involving (*a*) oxidation of the acyloin structure and (*b*) enolisation of the resulting α-diketone. Since bismuth acetate is known (Rigby, *J.*, 1951, 793; Holden and Rigby, *ibid.*, p. 1924) to be a specific reagent for step (*a*), its reaction with 3-hydroxyflavanones was investigated. **3** : 4′-Dihydroxy-**5** : 7-dimethoxyflavanone

* Part I, *J.*, 1954, 4065.

was oxidised almost quantitatively to 3 : 4′-dihydroxy-5 : 7-dimethoxyflavone (III; R = R‴ = H, R′ = R″ = Me); and 3-hydroxy-5 : 7 : 4′-trimethoxyflavanone gave the flavonol (III; R = H, R′ = R″ = R‴ = Me), identical with the product from the Allan–Robinson condensation of ω-benzoyloxy-2-hydroxy-4 : 6-dimethoxyacetophenone (IV) with *p*-anisic anhydride and potassium *p*-anisate. Selective demethylation of these compounds was achieved by fusion with aniline hydrochloride (Schonberg and Aziz, *J. Amer. Chem. Soc.*, 1953, **75**, 3265), 3 : 4′-dihydroxy-5 : 7-dimethoxyflavone yielding rhamnocitrin (III; R = R′ = R‴ = H, R″ = Me), and 3-hydroxy-5 : 7 : 4′-trimethoxyflavone giving 3 : 5-dihydroxy-7 : 4′-dimethoxyflavone (III; R = R′ = H, R″ = R‴ = Me). The last-named compound was also obtained, though in unexpectedly poor yield (cf. Part I), by partial methylation of kaempferide (III; R = R′ = R″ = H, R‴ = Me) with methyl sulphate and sodium hydrogen carbonate in acetone. On remethylation with methyl sulphate and aqueous-alcoholic sodium carbonate, 3 : 4′-dihydroxy-5 : 7-dimethoxy- and 3 : 5-dihydroxy-7 : 4′-dimethoxy-flavones yielded their 3-methyl ethers (III; R = R′ = R″ = Me, R‴ = H; and R = R″ = R‴ = Me, R′ = H).

The oxidation of flavanones to 3-hydroxyflavanones and thence to flavonols was next investigated. Naringenin (II; R = R′ = R″ = R‴ = H) was converted by methyl sulphate and sodium hydrogen carbonate in acetone (Part I) into its 7-methyl ether, sakuranetin, in 70% yield (cf. Narasimhachari and Seshadri, *Proc. Indian Acad. Sci.*, 1948, **27**, *A*, 227; Shinoda and Sato, *J. Pharm. Soc. Japan*, 1928, **48**, 933; *Chem. Abs.*, 1929, **23**, 2956). Oxidation with alkaline hydrogen peroxide then gave 3 : 5 : 4′-trihydroxy-7-methoxyflavanone (II; R = OH, R′ = R‴ = H, R″ = Me), the melting point of which is slightly higher than that reported by Uoda, Fukushima, and Kondô (*J. Agr. Chem. Soc. Japan*, 1943, **19**, 467; *Chem. Abs.*, 1951, **45**, 9136). Further methylation by methyl sulphate with aqueous alkali or potassium carbonate–acetone furnished the 7 : 4′-dimethyl ether, *OO*-dimethylkaturanin (Uoda *et al.*, and Goel *et al.*, *locc. cit.*); attempts to prepare this by peroxide oxidation of 5-hydroxy-7 : 4′-dimethoxyflavanone (II; R = R′ = H, R″ = R‴ = Me) proved unsuccessful, the product being apparently a difficultly separable mixture of benzylidenecoumaranone and hydroxyflavanone (cf. Geissman and Fukushima, *J. Amer. Chem. Soc.*, 1948, **70**, 1686).

Goel *et al.* (*loc. cit.*) failed to achieve the aerial oxidation of 3 : 5-dihydroxy-7 : 4′-dimethoxyflavanone in acid solution, dehydration yielding apigenin dimethyl ether. Oxidation with bismuth acetate has now given, normally, 3 : 5-dihydroxy-7 : 4′-dimethoxyflavone, identical with the previous specimen. In the same way, 3 : 5 : 4′-trihydroxy-7-methoxyflavanone was smoothly converted into rhamnocitrin.

Experimental

M. p.s were measured on a Kofler block and are corrected.

4 : 2′-*Dihydroxy*-4′ : 6′-*dimethoxychalkone* (I; R = R‴ = H, R′ = R″ = Me).—A solution of sodium hydroxide (12 g. in the minimum of boiled water), 2-hydroxy-4 : 6-dimethoxyacetophenone (5 g.), and *p*-hydroxybenzaldehyde (6 g.) in oxygen-free alcohol was refluxed under nitrogen for 30 min. The crude product, isolated by acidification of the cooled, diluted solution was recrystallised from ethanol, furnishing the *chalkone* in orange needles (4·8 g.), m. p. 194—196°, giving a dark brown ethanolic ferric colour [Found: C, 67·8; H, 5·2; OMe, 20·8. $C_{15}H_{10}O_2(OMe)_2$ requires C, 68·0; H, 5·4; OMe, 20·7%].

3 : 4′-*Dihydroxy*-5 : 7-*dimethoxy*- (II; R = OH, R′ = R″ = Me, R‴ = H) *and* 3-*Hydroxy*-5 : 7 : 4′-*trimethoxy*- (II; R = OH, R′ = R″ = R‴ = Me) *flavanone*.—The foregoing chalkone (500 mg.) was oxidised with hydrogen peroxide (100-vol; 1·3 ml.) in aqueous sodium hydroxide (5%; 25 ml.) at 0° overnight. The 3 : 4′-*dihydroxy*-5 : 7-*dimethoxyflavanone* precipitated on acidification recrystallised from ethanol as colourless rectangular tablets (350 mg.), m. p. 226—230°, which gave an intense cherry-red colour with zinc and concentrated hydrochloric acid but no ethanolic ferric reaction [Found: C, 64·7; H, 5·0; OMe, 19·7. $C_{15}H_{10}O_4(OMe)_2$ requires C, 64·6; H, 5·1; OMe, 19·6%].

Methyl sulphate (0·8 ml.) was added to a solution of the foregoing hydroxyflavanone (300 mg.) in alcohol (3 ml.), aqueous N-sodium carbonate (6 ml.), and N-sodium hydroxide (1 ml.).

The mixture was kept at 30° for 15 min. (crystals started to separate after 5 min.), diluted with water, and acidified. Recrystallisation from methanol gave *3-hydroxy-5 : 7 : 4′-trimethoxyflavanone* as colourless tablets (200 mg.), m. p. 141—143°, insoluble in aqueous sodium hydroxide, giving an intense red colour with zinc and concentrated hydrochloric acid and no ferric reaction in ethanol (Found : C, 65·5; H, 5·4. $C_{18}H_{18}O_6$ requires C, 65·4; H, 5·5%).

3 : 4′-Dihydroxy-5 : 7-dimethoxyflavone (III; R = R‴ = H, R′ = R″ = Me).—(*a*) A solution of 3 : 4′-dihydroxy-5 : 7-dimethoxyflavanone (1 g.) in aqueous sodium hydroxide (15%; 30 ml.) and " AnalaR " hydrogen peroxide (100-vol.; 2 ml.) was kept at 0° for 24 hr. and acidified. When twice recrystallised from acetic acid, the precipitate furnished the *flavonol* (III; R = R‴ = H, R′ = R″ = Me) in cream-coloured needles (300 mg.), m. p. 278—280°, giving a green-brown ferric colour in ethanol [Found : C, 65·1; H, 4·6; OMe, 19·5. $C_{15}H_5O_4(OMe)_5$ requires C, 65·0; H, 4·5; OMe, 19·7%]. Its *diacetate* formed colourless needles, m. p. 207—209°, from ethanol (Found : C, 63·4; H, 4·4. $C_{21}H_{18}O_8$ requires C, 63·3; H, 4·6%).

(*b*) A mixture of the 3-hydroxyflavanone (300 mg.), basic bismuth carbonate (600 mg.), 2-ethoxyethanol (12 ml.), and acetic acid (8 ml.) was gently refluxed for 1¼ hr., then filtered and the combined filtrate and washings were evaporated *in vacuo*. The resulting complex was dissolved in 10% aqueous sodium hydroxide and acidified with dilute hydrochloric acid. On recrystallisation from acetic acid, the pale yellow precipitate yielded 3 : 4′-dihydroxy-5 : 7-dimethoxyflavone in cream-coloured needles (230 mg.), m. p. and mixed m. p. 278—280°.

3-Hydroxy-5 : 7 : 4′-trimethoxyflavone (III; R = H, R′ = R″ = R‴ = Me).—(*a*) Hydrogen peroxide (100-vol.; 1·5 ml.) was added to the slurry from 3-hydroxy-5 : 7 : 4′-trimethoxyflavanone (500 mg.), ethanol (5 ml.), and aqueous sodium hydroxide (40%; 1 m.). After the vigorous reaction had ceased (10 min.) the mixture was diluted with water and acidified. Recrystallisation from methanol gave 3-hydroxy-5 : 7 : 4′-trimethoxyflavone as yellow needles (90 mg.), m. p. 149—150°, giving a green brown ethanol ferric colour [Found : C, 65·8; H, 4·9; OMe, 27·6. Calc. for $C_{15}H_7O_3(OMe)_3$: C, 65·9; H, 4·9; OMe, 27·8%]. Its acetate formed colourless needles, m. p. 193—194° (lit., 190—191°), from aqueous alcohol (Found : C, 65·1; H, 5·1. Calc. for $C_{20}H_{18}O_7$: C, 64·9; H, 4·9%).

(*b*) The 3-hydroxyflavanone (200 mg.) was refluxed with basic bismuth carbonate (400 mg.), 2-ethoxyethanol (6 ml.), and acetic acid (5 ml.), and the complex isolated, as in the previous experiment. Dissolution in warm methanol by the addition of 10% aqueous sodium hydroxide, acidification, and recrystallisation from methanol gave 3-hydroxy-5 : 7 : 4′-trimethoxyflavone in yellow needles (150 mg.), m. p. and mixed m. p. 149—150°.

(*c*) ω-Benzoyloxyphloroacetophenone (2·8 g.) (Heap and Robinson, *J.*, 1926, 2340) was refluxed with methyl sulphate (2·6 g.), potassium carbonate, and acetone for 5 hr. The *dimethyl ether* separated from light petroleum (b. p. 80—100°) in colourless needles (2·4 g.), giving a dark red ethanol ferric reaction (Found : C, 64·7; H, 5·2. $C_{17}H_{16}O_6$ requires C, 64·6; H, 5·1%). An intimate mixture of this ketone (1·5 g.), potassium *p*-anisate (1·5 g.), and *p*-anisic anhydride (9 g.) was heated to 170° for 2¾ hr. The melt was then hydrolysed with alcoholic potassium hydroxide, and the product isolated by the standard method. After repeated recrystallisation from methanol, 3-hydroxy-5 : 7 : 4′-trimethoxyflavone formed yellow needles (300 mg.), m. p. and m. p. on admixture with the product from (*a*) and from (*b*), 149—150°.

Rhamnocitrin (III; R = R′ = R‴ = H, R″ = Me) *and 3 : 5-Dihydroxy-7 : 4′-dimethoxyflavone* (III; R = R′ = H, R″ = R‴ = Me).—(*a*) An intimate mixture of 3 : 4′-dihydroxy-5 : 7-dimethoxyflavone (300 mg.) and aniline hydrochloride (500 mg.) was fused over a naked flame, heated in an oil-bath at 180° for 1 hr., cooled, and triturated with water. A portion of the insoluble material was chromatographed on Whatman No. 1 paper with benzene–pyridine–water (Simpson and Garden, *J.*, 1952, 4639) and found to contain rhamnocitrin and a small amount of kaempferol. Recrystallisation of the remainder from ethanol furnished rhamnocitrin in pale yellow needles or leaflets (120 mg.), giving an olive-green ethanolic ferric colour; the m. p. alone or on admixture with rhamnocitrin kindly supplied by Professor Seshadri was 221—223° (Found : C, 63·8; H, 4·1. Calc. for $C_{16}H_{12}O_6$: C, 64·0; H, 4·0%). Its triacetate separated from ethanol in colourless needles, m. p. 202° (Found : C, 62·0; H, 4·3. Calc. for $C_{22}H_{18}O_9$: C, 62·0; H, 4·3%).

(*b*) 3-Hydroxy-5 : 7 : 4′-trimethoxyflavone (200 mg.) was fused with aniline hydrochloride (700 mg.), and the product worked up as before. When thrice recrystallised from ethanol, *3 : 5-dihydroxy-7 : 4′-dimethoxyflavone* was obtained in yellow needles (85 mg.), m. p. 180—182°, giving an olive-green ethanolic ferric colour [Found : C, 65·1; H, 4·5; OMe, 19·9. $C_{15}H_5O_4(OMe)_3$ requires C, 65·0; H, 4·5; OMe, 19·7%]. Its *diacetate* formed colourless needles, m. p. 196—198°, from ethanol (Found : C, 63·4; H, 4·7. $C_{21}H_{18}O_8$ requires C, 63·3; H, 4·6%).

With an excess of methyl sulphate and potassium carbonate in boiling acetone during 24 hr., it yielded tetra-*O*-methylkaempferol in colourless plates, m. p. and mixed m. p. 164—165°.

(*c*) A mixture of kaempferide (500 mg.), sodium hydrogen carbonate (10 g.), methyl sulphate (210 mg.), and acetone (100 ml.) was refluxed with stirring for 48 hr. under carbon dioxide, and the product isolated by the standard method. Fractional crystallisation (from ethanol) of the alkali-insoluble portion furnished 3 : 5-dihydroxy-7 : 4′-dimethoxyflavone (30 mg.), m. p. 180—182°, and 5-hydroxy-3 : 7 : 4′-trimethoxyflavone (70 mg.), m. p. 152—153°.

5-Hydroxy-3 : 7 : 4′-trimethoxy- (III; R = R″ = R‴ = Me, R′ = H) *and 4′-Hydroxy-3 : 5 : 7-trimethoxy-flavone* (III; R = R′ = R″ = Me, R‴ = H).—Methyl sulphate (0·5 ml.) was added to a solution of 3 : 5-dihydroxy-7 : 4′-dimethoxyflavone (100 mg.) in alcohol (5 ml.) and aqueous N-sodium carbonate (8 ml.). After 15 min., the mixture was diluted with water and acidified and the solid recrystallised from ethanol. 5-Hydroxy-3 : 7 : 4′-trimethoxyflavone was obtained in pale yellow needles (70 mg.), m. p. and mixed m. p. 152—153° [Found : C, 65·7; H, 4·9; OMe, 28·2. Calc. for $C_{15}H_7O_2(OMe)_3$: C, 65·9; H, 4·9; OMe, 27·8%].

The alkali-soluble portion of the product from the similar methylation of 3 : 4′-dihydroxy-5 : 7-dimethoxyflavone (500 mg.) was repeatedly recrystallised from acetic acid, yielding 4′-hydroxy-3 : 5 : 7-trimethoxyflavone in pale yellow plates (30 mg.), m. p. 278—280°, giving no colour with ferric chloride and ethanol.

3 : 5 : 4′-Trihydroxy-7-methoxy- (II; R = OH, R′ = R‴ = H, R″ = Me) *and 3 : 5-Dihydroxy-7-4′-dimethoxy-flavanone* (II; R = OH, R′ = H, R″ = R‴ = Me).—Naringenin (3 g.), methyl sulphate (1·55 g., 1·1 mols.), anhydrous sodium hydrogen carbonate (20 g.), and acetone (100 ml.) were refluxed, with stirring, in carbon dioxide for 4 days. Isolation by the standard method and recrystallisation from aqueous ethanol and then from benzene yielded sakuranetin (II; R = H, R′ = R‴ = H, R″ = Me) in cream-coloured prisms (2·1 g.), m. p. 149·5—150·5°. A solution of this (500 mg.) in 2N-sodium hydroxide (20 ml.) and hydrogen peroxide (100-vol.; 1 ml.) was kept at 0°. Next day, more hydrogen peroxide (1 ml.) was added, and the mixture kept at 0° for a further 24 hr., then acidified with acetic acid. Recrystallisation from aqueous methanol gave 3 : 5 : 4′-trihydroxy-7-methoxyflavanone, pale yellow needles (320 mg.), m. p. 187—190°, giving a red-brown ferric colour in ethanol and an intense cherry-red colour with zinc and concentrated hydrochloric acid (Found : C, 63·4; H, 4·6. Calc. for $C_{16}H_{14}O_6$: C, 63·6; H, 4·7%).

The last-named compound (300 mg.) in alcohol (2 ml.), aqueous N-sodium carbonate (6 ml.), and N-sodium hydroxide (1 ml.) with methyl sulphate (0·8 ml.) (15 min.) gave 3 : 5-dihydroxy-7 : 4′-dimethoxyflavanone in colourless needles (150 mg.), m. p. 185—189° (from alcohol). Sparingly soluble in aqueous sodium hydroxide, it gave a red-brown ethanolic ferric colour, a cherry-red colour with zinc and concentrated hydrochloric acid, and a red colour with magnesium and concentrated hydrochloric acid (Found : C, 64·7; H, 4·9. Calc. for $C_{17}H_{16}O_6$: C, 64·6; H, 5·1%).

The same compound (80 mg.) was obtained from the hydroxyflavanone (150 mg.) by methyl sulphate (63 mg.) and potassium carbonate in acetone during 5 hr.

Rhamnocitrin and 3 : 5-Dihydroxy-7 : 4′-dimethoxyflavone.—3 : 5 : 4′-Trihydroxy-7-methoxyflavanone (100 mg.), basic bismuth carbonate (200 mg.), 2-ethoxyethanol (4 ml.), and acetic acid (3 ml.) were refluxed for 1¼ hr. and the complex was isolated and decomposed as before. Rhamnocitrin separated from ethanol in yellow needles (65 mg.), m. p. and mixed m. p. 221—223°.

3 : 5-Dihydroxy-7 : 4′-dimethoxyflavanone (50 mg.) similarly gave 3 : 5-dihydroxy-7 : 4′-dimethoxyflavone, yellow needles (30 mg.), m. p. and mixed m. p. 180—182°, from ethanol.

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The Chemistry of Hop Constituents. Part VII. Colupulone.†*

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The major constituent of the β-soft resin of some varieties of English hops has been shown to be the hitherto unrecognised colupulone (I; R = Pr^i). The degradations of this compound by hydrogenolysis, alkaline hydrogen peroxide, acid, and alkali are described and the results are compared with those obtained with lupulone (I; R = Bu^i). New structures are proposed for lupuloxinic acid (Howard and Pollock, *J.*, 1952, 1902) and its degradation products. Degradations of synthetic lupulone and colupulone confirm the various structures put forward.

An important crystalline component, lupulone, of the "β-soft resin" of hops, isolated as long ago as 1863 by Lermer (*J. prakt. Chem.*, 1863, **90**, 254), was formulated by Bungener (*Bull. Soc. chim.*, 1886, **45**, 487) and Barth and Lintner (*Ber.*, 1898, **31**, 2022) as $C_{25}H_{36}O_4$. Wöllmer (*Ber.*, 1925, **58**, 672) favoured the formula $C_{26}H_{38}O_4$ although the analytical data support equally either formulation.

Catalytic hydrogenation of lupulone was shown by Wöllmer (*loc. cit.*) to yield 3-methylbutane and a compound, $C_{21}H_{34}O_4$ (II; R = Bu^i), characterised as its crystalline tribenzoate, $C_{42}H_{46}O_7$, m. p. 164—165°. The hydrogenolysis product was oxidised by air in the presence of lead acetate to tetrahydrohumulone, $C_{21}H_{34}O_5$, m. p. 82—84° (III; R = Bu^i), which on alkaline hydrolysis furnished 4-methylpentanoic acid and dihydrohumulinic acid (IV; R = Bu^i). In view of the sequel it is interesting that Carson (*J. Amer. Chem. Soc.*, 1951, **73**, 1850) was also able to prepare tetrahydrohumulone having m. p. 82—83° from lupulone derived from American hops.

By contrast with the foregoing results the crystalline "β-resin" isolated from three samples of English hops afforded a hydrogenolysis product (II) which was different from that described by earlier workers as it yielded a tribenzoate, $C_{41}H_{44}O_7$, m. p. 134°. Further, this product was oxidised in good yield to a "tetrahydrohumulone" which although it was not obtained crystalline afforded by alkaline hydrolysis a compound which proved to be identical with dihydrocohumulinic acid (IV; R = Pr^i) (Howard and Tatchell, *J.* 1954, 2400). It thus follows that the "β-soft resin" used for the degradation must accordingly possess the structure (I; R = Pr^i). This compound is conveniently termed colupulone as it bears the same relation to lupulone as cohumulone does to humulone. Colupulone appears to be the major constituent of the β-soft resin of all samples of English hops examined by us and, indeed, no evidence of the presence of any authentic lupulone (I; R = Bu^i) has been obtained.

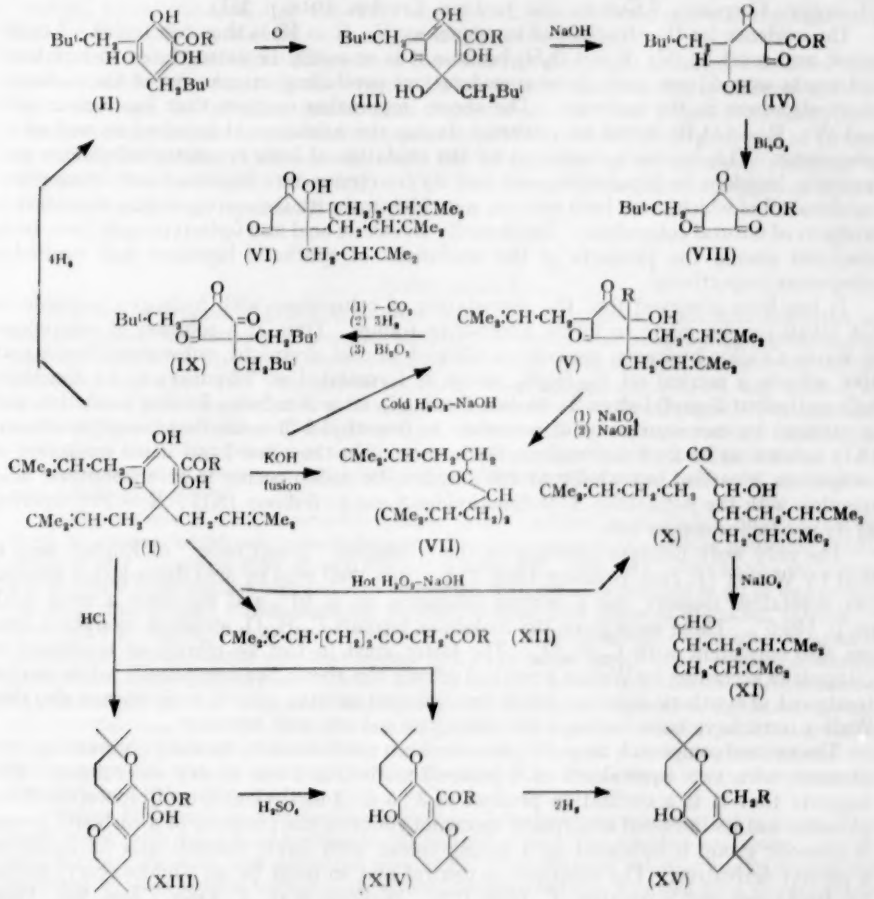
The material isolated from hops in the present work shows no depression of melting point when mixed with synthetic colupulone which had been incidentally prepared by Riedl (*Annalen*, 1954, **585**, 38) but exhibits a considerable depression with synthetic lupulone. By the methods already described, synthetic lupulone affords the tribenzoate of (II; R = Bu^i) having m. p. 164—165° as recorded by Wöllmer and by Carson (*locc. cit.*) whereas synthetic colupulone gives the tribenzoate of (II; R = Pr^i), having m. p. 134° identical with that from natural colupulone. Moerover, synthetic lupulone gives tetrahydrohumulone (III; R = Bu^i), m. p. 82—84°, whereas synthetic colupulone affords non-crystalline tetrahydrocohumulone (III; R = Pr^i).

Analytical results scarcely distinguish between lupulone and colupulone and their melting points are very similar, being 93° and 91—93° respectively (Riedl, *loc. cit.*). It is clear from degradative evidence that Wöllmer's material contained a high proportion of lupulone despite its low melting point (90·5—92°).

It will be recalled that Howard and Pollock (*loc. cit.*) showed that the oxidation of the crystalline "β-soft resin" of English hops by alkaline hydrogen peroxide affords crystalline

* Part VI, *J.*, 1954, 2400. † A preliminary account of part of this work has been reported (Howard and Pollock, *Chem. and Ind.*, 1954, 991).

lupuloxinic acid together with *iso*butyric acid. Whereas it was difficult to reconcile the production of the latter with the structure of lupulone its formation from colupulone clearly presents no problem. The initial oxidation of (I; R = Pr^{i}) is reminiscent of that of leptospermone (Briggs, Hassall, and Short, *J.*, 1945, 706) and directly affords *iso*butyric acid together with a product which is considered to undergo the type of ring-contraction encountered in the humulone series. Lupuloxinic acid is therefore formulated as (V;



R = CO_2H) while the product of its decarboxylation, lupulenol, becomes (V; R = H). Lupulenol was ascribed structure (VI) by Howard and Pollock (*loc. cit.*) on the grounds that it fails to reduce Fehling's solution, reacts as a monobasic acid, and reduces one equivalent of periodate to give a product which affords by alkaline hydrolysis a C_{18} ketone (VII). The failure to reduce Fehling's solution was regarded as precluding the presence of an acyloin group such as that in (V; R = H) and similar reasoning was applied to dihydrohumulinic acid (IV; R = Bu^{i}) in view of its failure to reduce the same reagent (Harris, Howard, and Pollock, *J.*, 1952, 1906). That the latter does in fact contain an acyloin group has, however, now been shown by oxidation with bismuth trioxide (cf. Rigby, *J.*, 1951, 793) to the corresponding α-diketone, *iso*humulinic acid (VIII; R = Bu^{i}) (cf. Harris, Howard, and Pollock, *loc. cit.*). The above conception of the formation and

structure of lupulenol is supported by the finding that hexahydrolupulenol is also smoothly oxidised by bismuth trioxide to a product having properties and light absorption consistent with its being 3 : 3 : 5-tri-3′-methylbutyl*cyclo*pentane-1 : 2 : 4-trione (IX). It is of interest that the sodium salt of this compound is insoluble in water and light petroleum though freely soluble in ethanol and quite soluble in ether. These unusual properties together with the analytical data suggest that this salt is a chelate compound, $C_{40}H_{67}O_6Na$, similar in character to those formed by compounds such as salicylaldehyde (cf. Ephraim, " Inorganic Chemistry," Gurney and Jackson, London, 1948, p. 351).

The evidence for the structure of lupulenol as (V; R = H) is thus conclusive. Lupuloxinic acid must be (V; R = CO_2H) because it is smoothly decarboxylated to lupulenol and reacts as a dibasic acid, these considerations precluding attachment of the carboxyl group elsewhere in the molecule. The above implication requires that lupuloxinic acid acid (V; R = CO_2H) would be produced during the oxidation of lupulone as well as of colupulone. This has been confirmed by the oxidation of both synthetic colupulone and synthetic lupulone to lupuloxinic acid and its conversion into lupulenol and hexahydrolupulenol all of which, from both sources, were identical with the corresponding degradation products of natural colupulone. Incidentally *iso*valeric acid and *iso*butyric acid have been identified among the products of the oxidations of synthetic lupulone and synthetic colupulone respectively.

It has been observed that the degradation of colupulone with hydrogen peroxide in hot alkali can be made to follow alternative routes. Thus, if a solution of colupulone in warm alkaline hydrogen peroxide is allowed to cool overnight, subsequent heating at 100° affords a neutral oil, $C_{19}H_{32}O_2$, which is formulated as 7-hydroxy-2 : 11-dimethyl-8-(3-methylbut-2-enyl)dodeca-2 : 10-dien-6-one (X), since it reduces Fehling's solution and is oxidised by one equivalent of periodate to 5-methyl-2-(3-methylbut-2-enyl)hex-3-enal (XI) isolated as its 2 : 4-dinitrophenylhydrazone. On the other hand if the oxidation of colupulone is carried out wholly at 100°, hydrolytic fission occurs to give *iso*butyric acid together with the β-diketone 2 : 9-dimethyldec-8-ene-3 : 5-dione (XII; R = Pr^i), isolated as its crystalline copper salt.

The only work hitherto recorded on the crystalline " β-soft resin " of English hops is that by Walker (*J. Inst. Brewing*, 1924, 712; 1949, 266) who by acid degradation isolated two crystalline isomers, one a neutral substance, m. p. 91°, and the other a weak acid, m. p. 169·5°. These were given the molecular formula $C_{21}H_{30}O_4$ although analytical data are also consistent with $C_{20}H_{28}O_4$. The latter must in fact be correct as treatment of colupulone according to Walker's method affords the above two compounds, while similar treatment of synthetic lupulone yields two different substances. It is significant also that Walker must have been dealing with colupulone and not with lupulone.

The neutral compound, m. p. 91°, has now been synthesised by treating phloro*iso*butyrophenone with two equivalents of 1-bromo-3-methylbut-2-ene in dry chloroform. This suggests that it is a cyclisation product of 3 : 5-di-(3-methylbut-2-enyl)phloro*iso*butyrophenone and its infra-red absorption spectrum confirms the presence of a carbonyl group. A phenolic group is indicated by a strong colour with ferric chloride and formation of a methyl derivative. The substance is neutral and so must be an *o*-hydroxyaryl ketone (cf. Backhouse and Robertson, *J.*, 1939, 1257; Wolfrom *et al.*, *J. Amer. Chem. Soc.*, 1946, **68**, 406); it is therefore 6-*iso*butyryl-3 : 4 : 9 : 10-tetrahydro-5-hydroxy-2 : 2 : 8 : 8-tetramethylbenzo[1,2-*b*, 3,4-*b*′]dipyran (XIII; R = Pr^i) (see Ring Index no. 1990). As the acidic isomer gives no colour with ferric chloride, contains one active hydrogen atom, and readily forms a monobenzoate and monomethyl ether, it is formulated as 10-*iso*butyryl-3 : 4 : 6 : 7-tetrahydro-5-hydroxy-2 : 2 : 8 : 8-tetramethylbenzo(1,2-*b*, 5,4-*b*′] dipyran (XIV; R = Pr^i) (Ring Index no. 1986). The ultra-violet absorption spectra of the two isomers in ethanol lend further support for those formulations (cf. Morton and Sawires, *J.*, 1940, 1052), and the close relation between the two compounds is borne out by the fact that the angular (XIII; R = Pr^i) is converted into the linear (XIV; R = Pr^i) by warm concentrated sulphuric acid. The acidic isomer undergoes reduction to a compound $C_{30}H_{30}O_3$, which is characterised as its monophenylurethane and mono-3 : 5-dinitrobenzoate and formulated as (XV; R = Pr^i). The chelate character of the hydroxy-ketone (XIII;

R = Pr^{i}) is further reflected by its failure to undergo similar reduction. The two compound obtained by acid degradation of synthetic lupulone are represented by the homologous formulations (XIII and XIV; R = Bu^{i}).

The presence of an *iso*valeryl side chain in lupulone was confirmed by Verzele and Govaert (*Bull. Soc. chim. Belg.*, **1949**, **48**, 432; *J.*, 1952, 1954) who isolated *iso*valeric acid from the alkaline fusion of both lupulone (I; R = Bu^{i}) and its hydrogenolysis product (II; R = Bu^{i}). The crystalline " β-resin " from English hops gives, in similar circumstances, *iso*butyric acid. At the same time, 6-methylhept-5-en-2-one and the high-boiling ketone (VII) (cf. Verzele and Govaert, *loc. cit.*) are also formed.

In this investigation, although at no time was *iso*valeric acid obtained, two other simple acids provisionally regarded as 2-methylbutanoic acid and 3-methylpentanoic acid were isolated from the alkaline fusion and characterised as their *p*-bromophenacyl esters. The occurrence of the former acid suggests the presence of a lupulone analogue of structure (I; R = CHMeEt). This accords with the recognition of adhumulone (Howard and Tatchell, *Chem. and Ind.*, **1954**, 992). The isolation of the second acid suggests that still another analogue of lupulone is present in hops.

Experimental.

Isolation of Crystalline β-Soft Resin from Hops.—Freshly ground hops were extracted with cold methanol, the suspension was filtered, and the filtrate was treated with methanolic lead acetate (18% w/v) to remove α-soft resin. The filtrate from the lead salt was diluted with brine and extracted with light petroleum (b. p. 40—60°), and the extract was washed with water, dried, and concentrated to low bulk in a vacuum under nitrogen. The crystalline material which separated at 0° was filtered off, washed with light petroleum, and recrystallized three times from light petroleum and then once from methanol. The product had m. p. 92—93°, undepressed on admixture with synthetic colupulone but depressed to 76—84° on admixture with synthetic lupulone.

Hydrogenolysis of Colupulone.—Colupulone (5 g.; isolated from Fuggle hops of the 1950 crop) in methanol (100 ml.) was hydrogenated in the presence of aqueous palladous chloride (3 ml. of 5%), absorbing 1080 ml. of hydrogen in 1 hr. ($4H_2$, 1100 ml.). One-half of the solution was evaporated to dryness and the residue treated with benzoyl chloride (3 g.) in dry pyridine (30 ml.); this yielded a *tribenzoate*, m. p. 133°, prisms from aqueous methanol (Found: C, 75·5; H, 7·1. $C_{41}H_{44}O_7$ requires C, 75·9; H, 6·9%). The remainder of the solution from the hydrogenation was treated with lead acetate (2·5 g.) in water (5 ml.) and the solution was then shaken with oxygen (absorption 70 ml.; $\frac{1}{2}O_2$, 70 ml.). The lead salt of tetrahydrocohumulone was filtered off (2·0 g., 74%) and decomposed with hydrogen sulphide in methanol, giving a yellow resin; $\lambda_{max.}$ 240, 285, and 325 mμ ($E^{1\%}_{1\,cm.}$ 265, 178, and 191 in EtOH), 230 and 325 mμ ($E^{1\%}_{1\,cm.}$ 395 and 335 in alkaline ethanol). In similar experiments with colupulone isolated from Bullion hops and from Fuggles hops, both of the 1953 crop, the yields of tetrahydrocohumulone were 46% and 80% respectively.

Alkaline Hydrolysis of Tetrahydrocohumulone.—Tetrahydrocohumulone (1·5 g.) was heated under reflux with 2N-sodium hydroxide (50 ml.) for 3 hr. The solution was cooled, acidified with hydrochloric acid, and extracted with ether. The ethereal solution was extracted with saturated aqueous sodium hydrogen carbonate; no material was removed by a further extraction with 2N-sodium hydroxide. The bicarbonate extracts yielded on acidification a mixture of acids which were isolated by means of ether. The resulting oil crystallized on treatment with aqueous methanol, affording dihydrocohumulinic acid, m. p. 89°, undepressed on admixture with material prepared by hydrogenating cohumulinic acid (Howard and Tatchell, *J.*, 1954, 2400) and depressed to 81° on admixture with dihydrohumulinic acid (Found: C, 66·3; H, 8·6; active H, 0·45. Calc. for $C_{14}H_{22}O_4$: C, 66·1; H, 8·7; 1H, 0·39%). On another occasion a portion of the hydrolysis product, insoluble in *cyclo*hexane, afforded, after crystallization from aqueous methanol, material of m. p. 152—153° which was not further examined.

Hexahydrolupulenol.—Colupulone (20 g.) was oxidised by alkaline hydrogen peroxide, and the product successively decarboxylated and hydrogenated (Howard and Pollock, *loc. cit.*), to give hexahydrolupulenol, m. p. 178° (9 g., 55% overall).

Oxidation of Hexahydrolupulenol with Bismuth Trioxide.—Hexahydrolupulenol (2 g.) and bismuth oxide (4 g.) were heated in refluxing acetic acid (25 ml.) for 24 hr., the suspension

was concentrated *in vacuo*, and the residue was diluted with ether and 2N-hydrochloric acid. The ethereal extract was washed with water, dried, and evaporated to leave an oil (2 g.). Distillation at 120° (bath-temp.)/10^{-4} mm. gave 3 : 3 : 5-3′-*methylbutyl*cyclo*pentane*-1 : 2 : 4-*trione* (1·8 g., 91%), m. p. 34° (Found : C, 74·5; H, 10·3. $C_{20}H_{34}O_3$ requires C, 74·6; H, 10·6%). Light absorption : In EtOH, $\lambda_{max.}$ 280 mμ (ε 9800); in alkaline ethanol, $\lambda_{max.}$ 230, 330 mμ (ε 12,500, 10,500); 3-3′-methylbutyl*cyclo*pentane-1 : 2 : 4-trione has $\lambda_{max.}$ 276 mμ (ε 12,250 in EtOH) and 233 and 328 mμ (ε 10,500 and 10,800 in alkaline ethanol) (cf. Howard and Pollock *loc. cit.*). The substance afforded a green copper complex, m. p. 114—115°. Shaking a solution of the compound in light petroleum with aqueous sodium hydrogen carbonate caused precipitation of a *sodium salt* (Found : C, 71·4; H, 10·2. $C_{40}H_{67}O_6Na$ requires C, 72·0; H, 10·1%) which was insoluble in water and light petroleum but readily soluble in ethanol and acetone and somewhat soluble in ether.

Oxidation of Dihydrohumulinic Acid with Bismuth Trioxide.—Dihydrohumulinic acid (122 mg.) and bismuth trioxide (140 mg.) were heated under reflux in acetic acid (10 ml.) for 24 hr. The cooled solution was diluted with 2N-hydrochloric acid (20 ml.) and extracted with ether. The ethereal extract was washed with water, dried, and evaporated. The residue was crystallized from methanol, to give *iso*humulinic acid (50 mg.), m. p. and mixed m. p. 143—144°.

Oxidation of Colupulone with Hot Alkaline Hydrogen Peroxide.—(i) Colupulone (10 g.) was dissolved in warm 10% aqueous sodium hydroxide (500 ml.), aqueous hydrogen peroxide (30%; 100 ml.) was added, and the solution allowed to cool to room temperature overnight. Then it was heated for 3 hr. on the steam-bath and steam-distilled. The product, isolated from the distillate by extraction with ether, was a yellow oil (2·75 g.). Distillation afforded 7-*hydroxy*-2 : 11-*dimethyl*-8-(3-*methylbut*-2-*enyl*)*dodeca*-2 : 10-*dien*-6-*one*, b. p. 178—182°/35 mm., n_D^{20} 1·4872, d_{20}^{20} 0·9000 [Found : C, 77·6; H, 10·7; active H, 0·31%; *M* (Rast), 302. $C_{19}H_{32}O_2$ requires C, 78·1; H, 10·9; 1H, 0·34%; *M*, 292], which reduced Fehling's solution, absorbed 2·7 mols. of hydrogen on hydrogenation, and reduced 0·97 equiv. of periodate, but failed to form a 2 : 4-dinitrophenylhydrazone or a semicarbazone.

(ii) Colupulone (20 g.) in warm 10% aqueous sodium hydroxide (1 l.) was treated with aqueous hydrogen peroxide (30%; 150 ml.). The solution was heated at 100° for 3 hr., cooled, and extracted with ether. The ethereal extract afforded no α-ketol. The aqueous layer was acidified with sulphuric acid and extracted with ether. The ethereal extract was shaken with saturated aqueous sodium hydrogen carbonate, and acids were isolated from the aqueous phase in the usual way. The ethereal phase was extracted with 2N-sodium hydroxide to remove enols. The acidic fraction was distilled, affording *iso*butyric acid (0·87 g.), b. p. 146—148°, and another fraction (0·73 g.), b. p. 150—166°/25 mm. (Found : equiv., by titration, 257). The enolic fraction was obtained as an oil (2 g.) which afforded a green *copper complex*, m. p. 214° (from ethanol) (Found : C, 66·3; H, 8·4; Cu, 14·6. $C_{24}H_{38}O_4Cu$ requires C, 63·5; H, 8·4; Cu, 14·0%). A solution of this complex (0·72 g.) in ether was shaken with 2N-sulphuric acid, and the ethereal phase washed with water, dried, and evaporated to yield 2 : 9-*dimethyldec*-8-*ene*-3 : 5-*dione* (Found : C, 73·2; H, 10·5%; equiv., by titration 195; p*K* in aqueous ethanol, 6·7. $C_{12}H_{20}O_2$ requires C, 73·5; H, 10·3%; equiv., 196). The compound afforded bromoform when treated with sodium hypobromite.

Periodate Oxidation of 7-*Hydroxy*-2 : 11-*dimethyl*-8-(3-*methylbut*-2-*enyl*)*dodeca*-2 : 10-*dien*-6-*one*.—The compound (1·33 g.), dissolved in methanol (50 ml.), was treated with sodium metaperiodate (1 g.) in water (15 ml.), and the solution kept for 24 hr. Sodium iodate (0·68 g.) was filtered off, and the filtrate was diluted with water and extracted with ether. The extract was washed with water, with aqueous sodium hydrogen carbonate, and again with water, dried, and evaporated to dryness. The residual oily 5-methyl-2-(3-methylbut-2-enyl)hex-3-enal yielded a 2 : 4-*dinitrophenylhydrazone*, which, after chromatography on alumina in benzene, was isolated as orange needles, m. p. 89·5° (Found : C, 59·6; H, 6·6; N, 15·6. $C_{18}H_{24}O_4N_4$ requires C, 60·0; H, 6·7; N, 15·6%).

Degradation of Colupulone under Acidic Conditions.—A solution of colupulone (10 g.) in methanol (500 ml.) and 12N-hydrochloric acid (150 ml.) was refluxed for 3·5 hr. (odour of isoprene) and then concentrated to 300 ml. The concentrate was extracted with ether (1 × 200; 2 × 100 ml.); the combined extracts were washed with water, dried, and evaporated. The residue was dissolved in light petroleum (b. p. 40—60°; 20 ml.) and the solution seeded and stored at 0° for 18 hr. The light petroleum solution was decanted and the crystals were washed with light petroleum and recrystallized from aqueous methanol, affording 10-iso*butyryl*-3 : 4 : 6 : 7-*tetrahydro*-5-*hydroxy*-2 : 2 : 8 : 8-*tetramethylbenzo*(1,2-b, 5,4-b′)*dipyran* (XIV; R = Pr^i)

(1·6 g.), m. p. 169·5° (Found: C, 72·0; H, 8·3; active H, 0·43. $C_{20}H_{28}O_4$ requires C, 72·3; H, 8·4; 1H, 0·3%). Light absorption: in concentrated H_2SO_4, $\lambda_{max.}$ 325 mμ (ε 24,500); in EtOH, 282 (ε 4000); in alkaline ethanol, 282 mμ (ε 4280); 5-hydroxy-7-methoxy-2 : 2-dimethyl-8-β-phenylpropionylchroman has $\lambda_{max.}$ 284 mμ (ε 5570; cf. Morton and Sawires, *loc. cit.*). The above light petroleum solution was chromatographed on alumina (Merck; washed with acetic acid and methanol), light petroleum (b. p. 40—60°) being the developing solvent. The rapidly moving yellow band was eluted and gave material which, recrystallized from aqueous methanol, afforded yellow plates of **6-iso*butyryl*-3 : 4 : 8 : 9-*tetrahydro*-5-*hydroxy*-2 : 2 : 8 : 8-*tetramethylbenzo*(1,2-b, 3,4-b′)*dipyran*** (XIII; R = Pr^i) (1·3 g.), m. p. 83° (Found: C, 71·9; H, 8·4; active H, 0·32. $C_{20}H_{28}O_4$ requires C, 72·3; H, 8·4; 1H, 0·3%). Light absorption in concentrated H_2SO_4, $\lambda_{max.}$ 325 mμ (ε 24,000); in EtOH, 298 mμ (ε 16,500); in alkaline ethanol, 300 mμ (ε 19,900); 7-hydroxy-5-methoxy-2 : 2-dimethyl-8-β-phenylpropionylchroman has $\lambda_{max.}$ 291 mμ (ε 18,700; cf. Morton and Sawires, *loc. cit.*). Methylation (cf. methylation of dihydro*iso*pomiferitin dimethyl ether, etc.; Wolfrom *et al.*, *loc. cit.*) afforded a resinous ***methyl ether*** (Found: C, 72·9; H, 8·7. $C_{21}H_{30}O_4$ requires C, 72·8; H, 8·7%).

The compound (XIV; R = Pr^i) is soluble in 12N-hydrochloric acid to give a deep yellow solution and in aqueous sodium hydroxide, but insoluble in aqueous sodium hydrogen carbonate; it forms a ***monobenzoate***, m. p. 159° (Found: C, 74·4; H, 7·5. $C_{27}H_{32}O_5$ requires C, 74·3; H, 7·4%), and a crystalline sodium salt but failed to react with phenyl *iso*cyanate. Methylation as for (XIII; R = Pr^i) afforded a ***methyl ether***, m. p. 134° (Found: C, 73·0; H, 8·7. $C_{21}H_{30}O_4$ requires C, 72·8; H, 8·7%). The isomer (XIII; R = Pr^i) was insoluble in alkali; it failed to react with benzoyl chloride in pyridine and absorbed no hydrogen on attempted hydrogen in the presence of palladous chlorde. Compound (XIII; R = Pr^i) exhibited maximal absorption at the following wave-lengths in the infra-red: 3·7 (w), 6·24 (s), 7·07 (m), 7·33 (m), 7·43 (m), 7·56 (m), 7·80 (m), 7·94 (m), 8·0 (s), 8·15 (m), 8·50 (m), 8·65 (s), 8·74 (s), 8·84 (s), 8·96 (s), 9·53 (w), 9·61 (w), 9·89 (w), 10·1 (w), 10·46 (m), 10·75 (w), 10·9 (w), 11·14 (w), 11·26 (w), 11·42 (w), 11·8 (w), 12·1 (w), 12·49 (w), 13·45 (w), 13·9 (w) and 14·6 (w) μ where (s) = strong, (m) = medium, (w) = weak. We are indebted to Professor Sir Alexander Todd, F.R.S., for this spectrum.

Hydrogenation of the Dipyran (XIV; R = Pr^i).—The compound (2 g.) was hydrogenated in methanol in the presence of palladous chloride, 274 ml. of hydrogen being absorbed ($2H_2$ and $C_{20}H_{28}O_4$ require 270 ml.). The solution was filtered and diluted with water, and **10-iso*butyl*-3 : 4 : 6 : 7-*tetrahydro*-5-*hydroxy*-2 : 2 : 8 : 8-*tetramethylbenzo*(1,2-b, 5,4-b′)*dipyran*** (XV; R = Pr^i) (1·7 g.) was filtered off. The compound recrystallized as colourless needles, m. p. 88°, from aqueous methanol (Found: C, 75·0; H, 9·7; active H, 0·28. $C_{20}H_{30}O_3$ requires C, 75·2; H, 9·5; 1H, 0·32%). The compound showed only end-absorption in the ultra-violet and formed a ***phenylurethane***, colourless prisms, m. p. 181—182°, from aqueous methanol (Found: C, 73·9; H, 8·2. $C_{27}H_{35}O_4N$ requires C, 74·1; H, 8·1%) and a **3 : 5-*dinitrobenzoate***, yellow plates, m. p. 221°, from aqueous methanol (Found: C, 62·8; H, 6·4; N, 5·6. $C_{27}H_{32}O_8N_2$ requires C, 63·1; H, 6·3; N, 5·5%).

Clemmensen Reduction of the Dipyran (XIV; R = Pr^i).—A solution of the compound (180 mg.) in 12N-hydrochloric acid (10 ml.) and ethanol (10 ml.) containing zinc amalgam (2 g.) was boiled under reflux for 2 hr. The colourless supernatant solution was diluted with water, and the product recrystallized from aqueous methanol to give the phenol (XV; R = Pr^i) (50 mg.), identical with the material prepared by catalytic hydrogenation of (XIV; R = Pr^i).

Isomerisation of the Angular Dipyran (XIII; R = Pr^i).—The yellow solution of the compound (0·5 g.) in concentrated sulphuric acid was warmed for 5 min. at 60° and poured on ice. The mixture was extracted with ether, and the ethereal extract shaken with saturated aqueous sodium hydrogen carbonate and with 2N-sodium hydroxide. The latter extract on acidification gave the isomer (XIV; R = Pr^i), m. p. 168° undepressed by material prepared directly from colupulone.

Alkaline Fusion of Crystalline β-Soft Resin.—(i) The material (10 g.) was dissolved in air-free 2N-potassium hydroxide (50 ml.), and solid potassium hydroxide (20 g.) was added. The mixture was distilled under nitrogen almost to dryness, water (40 ml.) added, and the mixture again distilled, the process being repeated five times. The residue was adjusted almost to neutrality with 12N-hydrochloric acid, silica filtered off, and the filtrate acidified with 2N-hydrochloric acid and saturated with sodium chloride. The solution was extracted with ether (3 × 100 ml.), and the extract was washed with saturated brine, dried (Na_2SO_4), and evaporated. The residue (4 g.) was distilled, the fraction of b. p. 146—178° (2·1 g.) being collected. Redistillation afforded (*a*) material, b. p. 152—156° (417 mg.), giving *p*-bromophenacyl *iso*butyrate, m. p.

and mixed m. p. 71°, and (*b*) material, b. p. 156—160°, n_D^{20} 1·4038 (389 mg.), giving a *p*-bromophenacyl ester, m. p. 54—55° (Found: C, 51·9; H, 4·7; Br, 27·2. Calc. for $C_{13}H_{15}O_3Br$: C, 52·1; H, 5·0; Br, 26·8%); *p*-bromophenacyl α-methylbutyrate has m. p. 55° (Murahashi, *Sci. Papers Inst. Phys. Chem. Research, Tokyo*, 1938, **34**, 155).

(ii) Crystalline β-resin (20 g.) was added to 2N-potassium hydroxide (100 ml.), and solid potassium hydroxide (40 g.) was added. The solution was evaporated nearly to dryness, water (100 ml.) added, and the process repeated four times. The distillate was extracted with light petroleum (b. p. 60—80°), and the extract dried and evaporated to dryness. Fractional distillation gave (*a*) a product (0·606 g.), b. p. 135—142°/28 mm., which gave a 2 : 4-dinitrophenylhydrazone which could not be crystallized, (*b*) 6-methylhept-5-en-2-one (0·4 g.), b. p. 170—172°/28 mm. (2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 78°), and (*c*) the ketone (VII) (1·148 g.), b. p. 160—185°/15 mm., n_D^{20} 1·4819, d_4^{20} 0·861. Howard and Pollock (*loc. cit.*) give b. p. 196°/40 mm., n_D^{12} 1·4832.

The residue from the fusion experiment was freed from silica as before and acidified. The acids, isolated as under (i) above, were distilled, affording (*a*) *iso*butyric acid, b. p. 150—158° (identified as the *p*-bromophenacyl ester), (*b*) an acid, b. p. 160—164°, and (*c*) an acid, b. p. 124—132°/45 mm. [*p*-bromophenacyl ester, m. p. 40° (Found: C, 53·3; H, 5·3; Br, 25·6. Calc. for $C_{14}H_{17}O_3Br$: C, 53·6; H, 5·4; Br, 25·6%)]. *p*-Bromophenacyl (±)-3-methylpentanoate has m. p. 36° (Sabetay and Panousse, *Compt. rend.*, 1945, **225**, 887).

Phloroisobutyrophenone.—A mixture of anhydrous phloroglucinol (19 g.), aluminium chloride (61 g.), and carbon disulphide (70 ml.) was stirred for 30 min., nitrobenzene (45 ml.) was then added, and the solution stirred and refluxed for a further 30 min. *iso*Butyryl chloride (16·4 g.) in nitrobenzene (5 ml.) was added to the boiling solution during 30 min. and the whole then stirred and heated for 1 hr. The thick syrup was poured into water (500 ml.), sodium potassium tartrate (500 g.) added, and the solution adjusted to neutrality. Volatile material was removed by steam-distillation (25 min.), the residue cooled until crystallization was complete, and the product filtered off. Recrystallization from water gave phloro*iso*butyrophenone (13 g., 44%), m. p. 78—82° (hydrate) or 138—140° (anhydrous).

Phloroisovalerophenone.—The compound, prepared from phloroglucinol and *iso*valeryl chloride in an analogous manner, had m. p. 145° (anhydrous).

Synthesis of Colupulone.—Phloro*iso*butyrophenone (6·67 g.) was converted into colupulone by Riedl's method (*loc. cit.*), giving 1·87 g. (14%) of pure product, m. p. 90—92°.

Synthesis of Lupulone.—Phloro*iso*valerophenone (15 g.) was similarly converted into lupulone (8·3 g., 29%), m. p. 89—90°, depressed to 76—82° on admixture with synthetic colupulone.

Hydrogenolysis of Synthetic Colupulone.—Synthetic colupulone (232 mg.) was hydrogenated in methanol in the presence of palladous chloride, the mixture filtered, and the filtrate evaporated to dryness *in vacuo*. The residue in pyridine (0·8 ml.) was treated with benzoyl chloride (0·4 g.), kept under nitrogen for 3 days, diluted with water, and extracted with ether, and the extract washed with dilute hydrochloric acid, saturated aqueous sodium hydrogen carbonate, and with water, dried, and evaporated. The product was crystallized from methanol and had m. p. 135—137°, undepressed on admixture with material similarly obtained from natural colupulone.

Hydrogenolysis of Synthetic Lupulone.—Synthetic lupulone (2·6 g.) was hydrogenated in methanol (70 ml.) containing palladous chloride, 592 ml. of hydrogen being absorbed ($4H_2$, 563 ml.). The mixture was filtered and a portion of the filtrate (20 ml.) benzoylated as above, giving material, m. p. 164—166° (Wöllmer, *loc. cit.*, gives m. p. 164—165°). Lead acetate (1·6 g.) was added to the remainder of the filtrate and the whole shaken with oxygen. The lead salt (1·542 g., 59%) was filtered off and decomposed with methanolic hydrogen sulphide, and the product isolated in the usual way. Recrystallized from aqueous acetic acid it had m. p. 82—84° (Wöllmer, *loc. cit.*, gives m. p. 82—84°).

Oxidation of Synthetic Colupulone with Alkaline Hydrogen Peroxide.—Synthetic colupulone (1·5 g.) was oxidised with hydrogen peroxide (30% w/v; 6 ml.) in 10% aqueous sodium hydroxide (75 ml.) as described previously (Howard and Pollock, *loc. cit.*). The non-volatile acidic product was decarboxylated by 5 minutes' boiling in toluene to material (420 mg., 33%), m. p. 117—119° undepressed on admixture with lupulenol obtained from natural colupulone. Hydrogenation of a portion (310 mg.) of the material in methanol over Adams's catalyst (uptake 74 ml. Calc. for $3H_2$ for $C_{20}H_{30}O_3$, 67 ml.) gave hexahydrolupulenol (226 mg.), m. p. 178—180° undepressed on admixture with material similarly prepared from natural colupulone. The volatile acid fraction of the oxidation was isolated in the usual manner and distilled. The distillate (114 mg.) gave *p*-bromophenacyl *iso*butyrate, m. p. and mixed m. p. 75—77°.

Oxidation of Synthetic Lupulone with Alkaline Hydrogen Peroxide.—Synthetic lupulone (5 g.) was oxidised in the usual manner. The volatile acidic material (730 mg.) had b. p. 172° and gave an anilide, m. p. 113—114°, and a *p*-bromophenacyl ester, m. p. 66—67°, both undepressed on admixture with the corresponding derivatives of *iso*valeric acid. The non-volatile acidic material (2·75 g.) was heated in boiling toluene (20 ml.) for 5 min., to give lupulenol (1·61 g.), m. p. 118—119° undepressed on admixture with material prepared from natural or synthetic colupulone. Hydrogenation of the material (1 g.) gave hexahydrolupulenol (1 g.), m. p. 176—178° undepressed on admixture with material prepared from natural or synthetic colupulone.

Synthesis of Compound (XIII; R = Pr^i).—To a suspension of phloro*iso*butyrophenone (3·25 g.) in chloroform (30 ml.), previously dried over phosphoric oxide, 1-bromo-3-methylbut-2-ene (4·93 g.) was added. Heat was evolved and hydrogen bromide was liberated while the phloro*iso*butyrophenone slowly dissolved. The clear solution was diluted with chloroform (40 ml.) and successively shaken with saturated aqueous sodium hydrogen carbonate, 2N-sodium carbonate, and N-sodium hydroxide. The extracted chloroform layer was evaporated to dryness, affording the dipyran (XIII; R = Pr^i) (0·349 g., 6·4%), m. p. 86—88°, undepressed by material prepared directly from colupulone.

Acid Degradation of Lupulone.—A degradation of synthetic lupulone (1·9 g.) carried out as for colupulone above afforded 3 : 4 : 6 : 7-*tetrahydro*-5-*hydroxy*-2 : 2 : 8 : 8-*tetramethyl*-10-β-*methylbutyrylbenzo*(1,2-b, 5,4-b′)*dipyran* (XIV; R = Bu^i), as colourless plates, m. p. 102—104° (0·67 g.), from aqueous methanol (Found: C, 72·7; H, 8·8. $C_{21}H_{30}O_4$ requires C, 72·8; H, 8·7%), and 3 : 4 : 8 : 9-*tetrahydro*-5-*hydroxy*-2 : 2 : 8 : 8-*tetramethyl*-6-β-*methylbutyrylbenzo*(1,2-b, 3,4-b′)*dipyran* (XIII; R = Bu^i), b. p. 155—160° (bath-temp.)/10^{-3} mm. (Found: C, 73·0; H, 8·8. $C_{21}H_{30}O_4$ requires C, 72·8; H, 8·7%).

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2-o-*Hydroxymethylphenyl*-2-*phenylpropan*-1-*ol and its Reaction with Hydrogen Bromide.*

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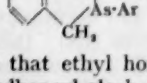
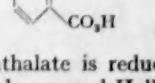
Reduction of α-methyl-α-phenylhomophthalic anhydride with lithium aluminium hydride has given 2-*o*-hydroxymethylphenyl-2-phenylpropan-1-ol. Subsequent reaction with hydrogen bromide resulted in a *neo*pentyl rearrangement accompanied by ring closure on to an aliphatic carbon atom to yield 3-methyl-2-phenylindene.

As part of a programme aiming at the demonstration of asymmetry arising from a tervalent arsenic atom, we attempted the synthesis of an unsymmetrically 4 : 4-substituted 2-aryl-1 : 2 : 3 : 4-tetrahydro*iso*arsinoline (I). We have been unsuccessful in this, but our experiments have shown an interesting rearrangement and ring closure.



(I)

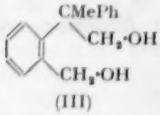


(II)

We previously showed that ethyl homophthalate is reduced by lithium aluminium hydride to *o*-2-hydroxyethylbenzyl alcohol (Anderson and Holliman, *J.*, 1950, 1037), thus providing a simple route to *o*-2-bromoethylbenzyl bromide (cf. Holliman and Mann, *J.*, 1942, 737). This dibromide is the penultimate stage in the synthesis of 1 : 2 : 3 : 4-tetra-

hydro*iso*arsinolines (Holliman and Mann, *J.*, **1943**, 547; Beeby, Cookson, and Mann, *J.*, 1950, 1917) and we have investigated an analogous approach to 4 : 4-disubstituted 1 : 2 : 3 : 4-tetrahydro*iso*arsinolines. We used the α-methyl-α-phenyl compound (II) synthesised by Koelsch, Hochman, and le Claire (*J. Amer. Chem. Soc.*, **1943**, **65**, 59), but modified the last two stages of the synthesis. In our hands, formaldehyde was satisfactory and more convenient than pyruvic acid in the hydrolysis of 2-hydroxyimino-3-methyl-3-phenylindan-1-one in spite of a statement to the contrary by these authors. Oxidation of the resulting 1 : 2-dione with hydrogen peroxide was found to be more readily effected by the method of Perkin, Roberts, and Robinson (*J.*, 1912, 234) than by that of Koelsch *et al.*; however, crystallisation of the crude product of this oxidation gives an acid which is always contaminated with the anhydride, so we have converted the product directly into the anhydride before purifying it. Attempts to resolve the acid were unsuccessful and we sought to prepare a derivative of the acid in which one of the carboxyl groups was blocked. With aniline the anhydride gave the *N*-phenylimide whilst with ethanol a mixture of the two monoethyl esters resulted; this mixture was successfully separated, but no attempt was made to orient the two esters.

With lithium aluminium hydride the anhydride gave very satisfactorily 2-*o*-hydroxymethylphenyl-2-phenylpropan-1-ol (III), which with hydrobromic acid under the conditions used by Holliman and Mann (*loc. cit.*) yielded a complex mixture: the main fraction was, unexpectedly, free from bromine, and after purification by chromatography had the formula $C_{16}H_{14}$ arising from the diol by the loss of two molecules of water. It had been expected that conversion of the diol into a dibromide might proceed with rearrangement of the *neo*pentyl type which would give (IV), (V), or (VI). Loss of two molecules of hydrogen bromide, one by ring closure on to the *ortho*-position of the phenyl group, would then be expected to give 9-ethylanthracene from (V); the m. p. of our hydrocarbon, however, was higher than that recorded for 9-ethylanthracene (Bradsher, *J. Amer. Chem. Soc.*, 1940, **62**, 486). An analogous elimination of hydrogen bromide from (IV) and (VI) would yield 3-methyl-1 : 2-5 : 6-dibenz*ocyclo*hepta-1 : 3 : 5-triene (VII). The absorption spectrum of the hydrocarbon showed bands at similar positions to, but with different intensities from, those reported for the methylenedibenz*ocyclo*heptatriene (VIII) (Bergmann *et al.*,

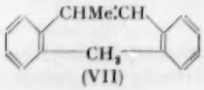

(III)

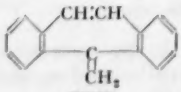
$Br{\cdot}CH_2{\cdot}C_6H_4{\cdot}CMeBr{\cdot}CH_2Ph$
(IV)

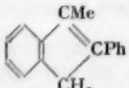
$Br{\cdot}CH_2{\cdot}C_6H_4{\cdot}CPhBr{\cdot}CH_2{\cdot}CH_3$
(V)

$Br{\cdot}CH_2{\cdot}C_6H_4{\cdot}CH_2{\cdot}CMePhBr$
(VI)

Bull. Soc. chim., 1951, 684) and was similar in shape to the spectrum of 1 : 2-diphenylprop-1-ene, but shifted to longer wave-lengths (Ramart-Lucas and Amagat, *ibid.*, 1932, **51**, 108). On the other hand, our spectrum was more closely similar to that of *trans*- rather than *cis*-stilbene (Smakula and Wasserman, *Z. physikal. Chem.*, 1931, *A*, **155**, 353;


(VII)

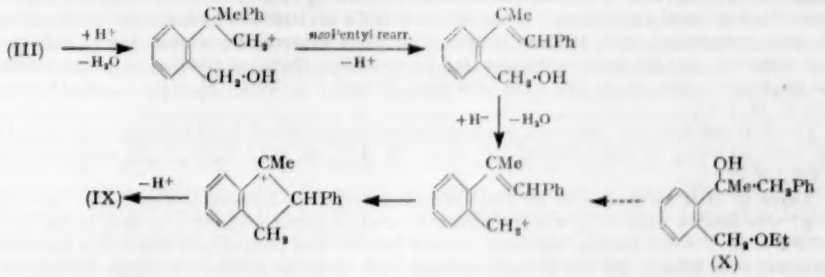

(VIII)


(IX)

Lewis, Magel, and Lipkin, *J. Amer. Chem. Soc.*, 1940, **62**, 2973), and, furthermore, non-identity with (VII) was indicated by oxidation with chromic acid to benzoic acid instead of the benzophenone derivative to be expected from (VII) (cf. Treibs and Klinkhammer, *Chem. Ber.*, 1951, **84**, 671). The spectroscopic and degradative evidence suggested that our hydrocarbon might be 3-methyl-2-phenylindene (IX); this supposition was strengthened by the agreement between the m. p. (76—78°) of our compound and that (74—75°) reported for (IX) (*inter al.*, Blum-Bergmann, *Ber.*, 1932, **65**, 109) and confirmed through the m. p. (180—182°) of the hydroxyimino-derivative (Blum-Bergmann, *loc. cit.*, m. p. 184—185°). The absorption spectrum of (IX) has been recorded only above 326 mμ by

Ramart-Lucas and Salmon-Legagneur (*Bull. Soc. chim.*, 1929, **45**, 718) who wrongly considered it to be 9 : 10-dimethylanthracene (Blum-Bergmann, *loc. cit.*); in this region, only end-absorbtion is observed and comparison with our spectrum was of no value.

A possible mechanism for the formation of 3-methyl-2-phenylindene from the diol (III) and involving the attack of a carbonium ion on an olefinic linkage rather than on an aromatic nucleus, is as annexed. Schmerling (*J. Amer. Chem. Soc.*, 1945, **67**, 1152; 1946, **68**, 1650, 1655; 1947, **69**, 1121; 1949, **71**, 698, 701, 753) has shown that alkyl halides add to an olefinic linkage in the presence of aluminium chloride and similar catalysts, probably owing to the initial attack by a carbonium ion on the olefinic system (Alexander, " Ionic Organic Reactions," J. Wiley and Sons, New York, 1950, pp. 143—146); generally, this was followed by addition of the halogen ion, but in a few instances by elimination of a proton, resulting in alkylation of the olefin. Our cyclisation presumably follows the second course on account of the conjugation of the double bond with two aromatic nuclei. On our suggested mechanism it seemed probable that 3-methyl-2-phenylindene would result from the action of hydrobromic acid on other substances which, under these condi-



tions, might be expected to enter this pathway. To test this hypothesis, 2-*o*-ethoxymethylphenyl-1-phenylpropan-2-ol (X) was synthesised. With hydrobromic acid under similar conditions to those used on the diol (III) it gave the hydrocarbon in yield similar to that previously obtained.

These experiments have suggested the possibility of alkylating olefins by means of alcohols in the presence of acids. Preliminary experiments involving stilbene and methyl alcohol in the presence of hydrobromic or sulphuric acid have been unsuccessful but other alcohols and catalysts are being investigated.

Experimental

The stages up to and including 2-hydroxyimino-3-methyl-3-phenylindanone were as described by Koelsch *et al.* (*loc. cit.*).

3-Methyl-3-phenylindan-1 : 2-dione.—2-Hydroxyimino-3-methyl-3-phenylindanone (265 g.) and 40% aqueous formaldehyde (600 c.c.) were heated, with stirring, with concentrated hydrochloric acid (120 c.c.) for 30 min. on the water-bath, then kept overnight. The orange, solid-containing mixture was heated on the water-bath, with stirring, during 48 hr., formaldehyde and concentrated hydrochloric acid being added from time to time. After cooling, the orange crystalline material was collected, washed well with water, and recrystallised from ethanol (yield 229 g., 92%; m. p. 113—116°).

α-Methyl-α-phenylhomophthalic Anhydride.—A solution of the above diketone (50 g.) in warm methanol (1500 c.c.) was rapidly chilled with vigorous stirring to give a fine suspension. 3% Hydrogen peroxide (500 c.c.) was added, followed (dropwise) by sodium carbonate (30·6 g.) in water (200 c.c.). Chilling and stirring were continued during 3 hr. and the mixture was then set aside overnight. The methanol was removed under reduced pressure and the residue dissolved in water. After extraction with ether, the aqueous solution was combined with aqueous sodium carbonate washings of the ethereal extract, and the mixture was acidified. The precipitated acid was extracted with chloroform, the solvent removed from the extract, and the residue heated at 140° during 3 hr. Recrystallisation of the resulting *anhydride* from light

petroleum (b. p. 40—60°) gave 35 g. (65%) of colourless prisms, m. p. 67—68·5° (Found: C, 76·0; H, 4·8. $C_{16}H_{12}O_3$ requires C, 76·2; H, 4·8%).

Heating the anhydride with excess of aniline at 160° for 2 hr. and adding hydrochloric acid to the cooled mixture gave a solid which was insoluble in aqueous sodium carbonate solution. Recrystallisation from ethanol gave α-*methyl*-α: N-*diphenylhomophthalimide*, m. p. 114·5—115·5° (Found: C, 80·5; H, 5·2. $C_{22}H_{17}O_2N$ requires C, 80·7; H, 5·2%).

A mixture of the two isomeric *monoethyl esters* of α-methyl-α-phenylhomophthalic acid was prepared (*a*) by refluxing the anhydride with excess of ethanol in the presence of pyridine for 20 hr., and (*b*) by heating the anhydride with excess of ethanol in a sealed tube at 155° for 7 hr. Acidification gave a gum which slowly crystallised, then having m. p. 103—109°. Fractional crystallisation from light petroleum (b. p. 60—80°) gave approximately equal quantities of the two isomeric esters: (i) m. p. 125—127° (Found: C, 72·7; H, 6·2. $C_{18}H_{18}O_4$ requires C, 72·4; H, 6·1%); (ii) m. p. 129·5—132° (Found: C, 72·7; H, 6·2%). The mixed m. p. of (i) and (ii) was 100—116°.

2-o-*Hydroxymethylphenyl*-2-*phenylpropan*-1-*ol*.—A solution of α-methyl-α-phenylhomophthalic anhydride (60 g.) in ether (500 c.c.) was added during 3 hr. to finely powdered lithium aluminium hydride (25 g. of commercial material containing 71% of the active reagent) suspended in ether in the usual apparatus. After refluxing for 3 hr., the mixture was set aside overnight and then hydrolysed with 10% sulphuric acid. The ethereal layer was dried (K_2CO_3), the ether removed, and the residue fractionated to give 55 g. (95%) of the *diol* as a highly viscous, blue-fluorescent glass, b. p. 185—188°/0·6 mm. (Found: C, 79·5; H, 6·8. $C_{16}H_{16}O_2$ requires C, 79·3; H, 7·5%).

The *di*-p-*nitrobenzoate*, prepared in pyridine and recrystallised from ethanol, had m. p. 162—164° with sintering at 132° (Found: C, 67·0; H, 4·5; N, 5·4. $C_{30}H_{24}O_8N_2$ requires C, 66·7; H, 4·5; N, 5·2%).

Action of Hydrobromic Acid on 2-o-*Hydroxymethylphenyl*-2-*phenylpropan*-1-*ol*.—The alcohol (19 g.) was heated with 50% w/v hydrobromic acid in acetic acid (80 c.c.) in a sealed tube at 100° for 11 hr. After cooling, the dark, viscous product was poured into water, the mixture was extracted with ether, and the extract washed with aqueous sodium hydrogen carbonate and dried ($MgSO_4$). The ether was removed and the residue fractionated to give fractions: (*a*) 7 g., b. p. 140—144°/0·6 mm., and (*b*) 3 g., b. p. 160—175°/0·6 mm. Fraction (*b*) gave a positive test for halogen but was non-lachrymatory, and did not yield a definite product. Fraction (*a*) gave a negative test for halogen and eventually crystallised. It was chromatographed in light petroleum on alumina and gave several fluorescent bands. The major band was not strongly absorbed and was eluted in light petroleum, to give 3·5 g. of a crystalline hydrocarbon, m. p. 76—78° after recrystallisation from ethanol (Found: C, 93·3; H, 6·8. Calc. for $C_{16}H_{14}$: C, 93·2; H, 6·8%). The absorption spectrum of an alcoholic solution showed maxima at 228 (ε 10,230) and 294 mμ (ε 19,950), and solutions in light petroleum had a strong blue fluorescence.

2-o-*Ethoxymethylphenyl*-1-*phenylpropan*-2-*ol* (X).—*o*-Bromobenzyl ethyl ether (29 g.) in anhydrous ether (80 c.c.) was converted into the Grignard reagent by using 7·2 g. of activated magnesium powder and 3·6 c.c. of ethyl bromide (Holliman and Mann, *loc. cit.*). Phenylacetone (24 g.; *Org. Synth.*, **16**, 47) in ether (100 c.c.) was added, with stirring, at such a rate that gentle refluxing was maintained. The mixture was refluxed during 3 hr., set aside overnight, and poured on crushed ice and dilute sulphuric acid. The aqueous layer was extracted three times with ether and the combined ethereal solutions were dried (K_2CO_3). Removal of the ether and fractionation of the residue gave 26 g. (69%) of the *alcohol* at 143—144°/0·3 mm. (Found: C, 80·1; H, 8·2. $C_{18}H_{22}O_2$ requires C, 80·0; H, 8·15%).

The alcohol (7 g.) and 50% w/v hydrobromic acid in acetic acid (40 c.c.) were heated in a sealed tube at 100° for 11 hr. The cooled mixture was poured into water and extracted with ether. The ethereal solution was washed with sodium carbonate solution and, after drying ($CaCl_2$), the ether was removed and the product was fractionated. The main fraction (b. p. 130—148°/0·1 mm.; 1·4 g., 26%) solidified, and was recrystallised from alcohol to yield leaflets, m. p. 74—76° unchanged on admixture with 3-methyl-2-phenylindene.

UNIVERSITY OF CAPE TOWN, SOUTH AFRICA. [*Received, September 18th*, 1954.]

Isomeric N-*Arylglycosylamine Tetra-acetates.*

By R. Bognár and P. Nánási.

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It is confirmed that a mixture of dextro- and lævo-rotatory isomers is formed in the preparation of *N*-arylglycosylamine tetra-acetates by a number of methods. Syntheses of seven such dextro- and lævo-rotatory compounds are recorded. The isomeric—probably anomeric—forms are interconvertible in solution and exhibit mutarotation in the presence of acid to reach an equilibrium. Structural problems and reactions of these compounds, which probably contain the strainless chair conformation of the pyranoside, are discussed.

In a previous paper it was recorded (Bognár and Nánási, *J.*, 1953, 1703) that reaction of acetobromoglucose or of D-glucose 2 : 3 : 4 : 6-tetra-acetate with sulphanilamide, or transglucosylation (*idem*, *Nature*, **1953**, **171**, 475) of *N*-phenyl-D-glucosylamine 2 : 3 : 4 : 6-tetra-acetate with sulphanilamide in alcoholic hydrochloric acid, yields a mixture of two isomeric—probably anomeric—N^4-*p*-sulphamylphenyl-D-glucosylamine tetra-acetates. We now report formation and separation of other, similar *N*-arylglycosylamine tetra-acetates by (*a*) acetylation of *N*-arylglycosylamines in pyridine, and by reaction of an aromatic amine with (*b*) an acetobromo-sugar, (*c*) an acetylated aldopyranose, (*d*) a partly acetylated aldopyranose (*e.g.*, D-glucose 2 : 3 : 4 : 6-tetra-acetate), or (*e*) an acetylated *N*-arylglycosylamine (transglycosylation). All these methods give mixtures of anomers, but in proportions varying according to the method. One of the anomers is often formed in higher yield and is then isolated without difficulty, while separation of the other may be tedious.

Our results agree well with previous records on the preparation of isomeric glycosylamine tetra-acetates, *e.g.*, *N*-phenyl-D-glucosylamine tetra-acetate (Honeyman and Tatchell, *J.*, **1950**, 967, and Pigman and Johnson, *J. Amer. Chem. Soc.*, **1953**, **75**, 3464, methods *a* and *c*; Frèrejacque, *Compt. rend.*, 1936, **222**, 1190; 1937, **204**, 1480, and Weisz, Diss., Budapest, 1940, method *c*; Weisz, *loc. cit.*, method *d*), *N*-phenyl-D-galactosylamine tetra-acetate (Butler, Smith, and Stacey, *J.*, 1949, 3371, methods *a* and *d*), *N*-(4-chloro-2-nitrophenyl)-α- and -β-glucosylamine tetra-acetate, -α- and -β-D-xylosamine triacetate, and -α- and -β-D-arabinosylamine triacetate (Antaki and Petrow, *J.*, **1951**, 2873, method *a*). Not only the α- and β-anomers of N^4-*p*-sulphamylphenyl-D-glucosylamine tetra-acetate have been isolated but other isomeric pairs as well, though Butler *et al.* (*loc. cit.*) and Ellis and Honeyman (*J.*, 1952, 2053) reported merely that a small quantity of the α-anomer appears to be formed by method (*b*) along with the main product, the β-anomer. Our results are tabulated on p. 188.

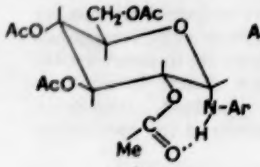
Mutarotation of the tetra-acetates does not occur in dry pyridine; in methanol it occurs slowly in some cases (*e.g.*, *N*-*p*-tolyl-D-glucosylamine or -mannosylamine tetra-acetate), but it is always very rapid (complete within a few minutes) in 0·1N-methanolic hydrogen chloride at room temperature. The α-anomers, otherwise difficulty accessible, are then relatively readily separated from the resulting mixture of the anomers.

The *N*-*p*-tolyl-D-glucosylamine tetra-acetate obtained by Ellis and Honeyman (*loc. cit.*) by method (*a*) is a mixture of anomers readily separable into its components by crystallisation. A similar mixture was obtained by method (*b*) in acetone containing sodium hydroxide.

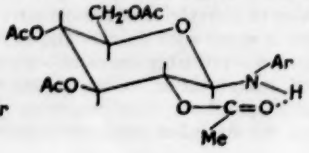
Acetic anhydride in the presence of anhydrous zinc chloride converts both anomers of *N*-*p*-tolyl-D-glucosylamine tetra-acetate into the same penta-acetate. Similarly *N*-*p*-sulphamylphenyl-D-mannosylamine tetra-acetate gives a hexa-acetate. The structures of these compounds and of the known *N*-phenyl-D-glucosylamine *N* : 2 : 3 : 4 : 6-penta-acetate and *N*-*p*-sulphamylphenyl-D-glucosylamine *N* : *N* : 2 : 3 : 4 : 6-hexa-acetate (Bognár and Nánási, *loc. cit.*) remain uncertain although these compounds are dextrorotatory: attempts at deacetylation and at their preparation from *N*-acetylarylamines by methods (*a*)—(*e*) failed.

Hudson's isorotation rule applies to some of our anomers and allows correlations of the pure α- and β-anomers.

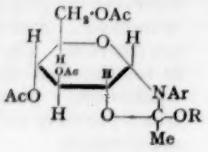
It was suggested in previous papers that the more soluble α-tetra-acetates might be stabilised by hydrogen bonding between the nitrogen atom and the carbonyl-oxygen atom of the 2-acetoxy-group. In fact similar hydrogen-bond formation cannot be excluded for the β-anomer if the sugar is in the strainless chair conformation. However, stabilisation



α-Anomer



β-Anomer



of the acetates in an oxazolidine system is also conceivable. The mutarotation in acid, deacetylation, and acetylation of the tetra-acetates (giving identical derivatives from the anomers) would involve reversible fission of both the oxazolidine and the pyranose ring.

Experimental

N-p-*Tolyl*-D-*glucosylamine* 2 : 3 : 4 : 6-*Tetra-acetates.*—*Method* (*a*). *N*-*p*-Tolyl-β-D-glucosylamine (Weygand, *Ber.*, **1939**, **72**, 1666) (8·0 g.) was treated in pyridine (35 ml.) and acetic anhydride (20 ml.) with cooling. The mixture was kept for 2 days at room temperature, then poured into ice-water (400 ml.). The crude product (12 g., 92%) had $[\alpha]_D^{22}$ +25·5° (*c*, 0·9 in pyridine). Recrystallisation of 8 g. from 96% alcohol (30 ml.) gave product " A " (4·9 g.), m. p. 148°, $[\alpha]_D^{22}$ −63·5°. On addition of water to the alcoholic mother-liquors, product " B " (2·4 g.) crystallised, having m. p. 129°, $[\alpha]_D^{22}$ +114°. Product " A," recrystallised from a ten-fold quantity of methanol, yielded the pure β-isomer (2 g.) (see Table for this and other pure isomers). Product " B " was recrystallised twice from alcohol, and the substance remaining in the mother-liquor was precipitated with water and crystallised from methanol, giving the pure α-anomer (0·12 g.).

(*b*) *p*-Toluidine (6·0 g., 1 mol.) and acetobromoglucose (30·0 g., 1·2 mols.) in acetone were treated with 10% sodium hydroxide solution (30 ml.) with shaking during 90 min. The mixture was shaken for 2 days, then part of the acetone was removed *in vacuo*. This afforded product " A " (4·1 g.), m. p. 130—132°, $[\alpha]_D$ −54° in pyridine. Addition of water to the mother-liquor gave the crystalline product " B " (3·9 g.), m. p. 125—130°, $[\alpha]_D$ +32° in pyridine. Product " A " (4·0 g.) crystallised from 96% alcohol (30 ml.), to yield the pure β-anomer (1·8 g.). Product " B " (3·9 g.) crystallised from alcohol to give a substance (1·1 g.), of $[\alpha]_D$ −77°. This (1 g.) was recrystallised twice from alcohol giving a further 0·75 g. of β-anomer. When water was added to the alcoholic mother-liquor a substance (0·95 g.) separated having $[\alpha]_D$ +91° in pyridine. This purification was repeated several times and the substance which separated from the aqueous alcohol was finally crystallised from a ten-fold quantity of methanol to yield the pure α-anomer as needles (0·21 g.) (Found : C, 57·65; H, 6·3; N, 3·2, 3·2. $C_{21}H_{27}O_9N$ requires C, 57·7; H, 6·2; N, 3·2%).

(*c*) Penta-*O*-acetyl-D-glucose (10·0 g., 1 mol.) in 99% alcohol (200 ml.) and glacial acetic acid (10 ml.) was treated with *p*-toluidine (10·0 g., 4 mols.). After 24 hr. crystallisation began on scratching. The product " A " (8·6 g.) had m. p. 145° and $[\alpha]_D$ −67° in pyridine. This (4·5 g.) crystallised from 96% alcohol (30 ml.), to yield pure β-anomer (3·2 g.). The crude substance (3·5 g.) precipitated from the mother-liquor by water was recrystallised from alcohol. This alcoholic mother-liquor yielded with water the α-anomer (1·5 g.), m. p. 126—127°, $[\alpha]_D^{22}$ +82° in pyridine, which could be purified further.

(*d*) Tetra-*O*-acetyl-D-glucopyranose (5·0 g., 1 mol.) and *p*-toluidine (4·0 g., 3 mols.) in 99% alcohol (30 ml.) were boiled for 1 hr. On cooling to 0° a product (0·7 g.) " A " separated, m. p. *ca.* 141°, $[\alpha]_D$ −46·9° in pyridine. Water was added to the mother-liquor until it became turbid; product " B " separated (0·65 g.) which showed no rotation. A further product (1·7 g.), $[\alpha]_D$ +80°, was obtained from the mother-liquor and yielded on recrystallisation from alcohol 0·43 g. of a substance of $[\alpha]_D$ +130°. Repeated crystallisation from methanol led to the pure α-anomer.

N-p-*Tolyl*-D-*glucosylamine* N : 2 : 3 : 4 : 6-*Penta-acetate*.—The α- and the β-tetra-acetate were severally treated with acetic anhydride (10 pts.) and zinc chloride (0·5 pt.) for 15 min. on the water-bath, then poured into cold water. The crude products were recrystallised from aqueous alcohol. A mixture of the two penta-acetates thus obtained showed no depression of the m. p. (143°); $[\alpha]_D^{22}$ +50·4° (*c*, 0·9 in pyridine), +63·3° (*c*, 1·1 in $CHCl_3$) (Found : C, 57·7; H, 6·2; N, 2·9, 2·9. Calc. for $C_{23}H_{29}O_{10}N$: C, 57·6; H, 6·11 N, 2·9%). Weisz (*loc. cit.*) gives m. p. 142°, $[\alpha]_D$ +64·2° in $CHCl_3$.

N-p-*Bromophenyl*-D-*glucosylamine* 2 : 3 : 4 : 6-*Tetra-acetates*.—*Method* (*b*). *p*-Bromoaniline (2·3 g., 1 mol.) and acetobromoglucose (6·5 g., 1·2 mols.), treated in acetone with 10% sodium hydroxide solution (6·5 ml.) during 30 min., gave two layers. The mixture was shaken for 2 days, the solvent removed *in vacuo*, and the oily residue crystallised from alcohol (20 ml.), to yield product " A " (2·5 g.), $[\alpha]_D$ −48·3° in pyridine. Product " B " (1·9 g.), $[\alpha]_D$ +50° in pyridine, was separated from the mother-liquor on addition of water. Product " A " was twice recrystallised from 90% alcohol, to yield the pure β-anomer (1·5 g.). Product " B " was crystallised from alcohol, and water added to the mother-liquor. The precipitated α-*anomer*, purified by repeated fractionation with alcohol and water, and then by crystallisation from ether–light petroleum, had m. p. 150—152° (0·12 g.) (Found : C, 46·8; H, 4·6; N, 2·8. $C_{20}H_{24}O_9NBr$ requires C, 47·8; H, 4·8; N, 2·8%).

Method (*d*). *p*-Bromoaniline (2·5 g., 2·5 mols.) and tetra-*O*-acetyl-D-glucose (2 g., 1 mol.) were boiled for 1 hr. in 99% alcohol, to yield a mixture of dextro- and lævo-rotatory *N*-*p*-bromophenyl-D-glucosylamine 2 : 3 : 4 : 6-tetra-acetates. A product with m. p. 160—162° and $[\alpha]_D^{22}$ −64·2° (*c*, 1·2 in pyridine) and another with $[\alpha]_D$ +100°, containing much of the dextrorotatory isomer, were isolated in the usual way.

N-(3-*Hydroxy*-4-*propoxycarbonylphenyl*)-D-*glucosylamine* 2 : 3 : 4 : 6-*Tetra-acetates*.—*Method* (*b*). Propyl 4-aminosalicylate (2·0 g., 1 mol.) and acetobromoglucose (4·5 g., 1·1 mols.) reacted in the usual way in acetone (20 ml.) in the presence of 10% sodium hydroxide solution. The mixture was shaken for a day, the solvent removed, and the residue washed with water and crystallised from 96% ethanol (5 ml.). After precipitation of a part of the unchanged ester (0·35 g.) water was added. The oil thus obtained crystallised from aqueous alcohol (product " A "; 0·6 g.). Addition of water to the mother-liquor from " A " yielded a fraction " B " (0·9 g.). Product " A ", twice crystallised from alcohol (5 ml.), afforded 0·35 g. of pure β-*anomer* (Found : N, 2·6. $C_{24}H_{31}O_{12}N$ requires N, 2·7%). A lævorotatory product was also obtained from product " B," but the mother-liquors therefrom yielded a dextrorotatory substance after further crystallisation.

Method (*d*). Propyl 4-aminosalicylate [(i) 1·2, (ii) 1·5 mols.] was treated in absolute alcohol with D-glucose 2 : 3 : 4 : 6-tetra-acetate (1 mol.) in the presence of small quantities of (i) concentrated hydrochloric acid and (ii) acetic acid. Working up in the usual way gave the β- and the α-*anomer* (Found : N, 2·8%).

N-p-*Sulphamylphenyl*-D-*mannosylamine* 2 : 3 : 4 : 6-*Tetra-acetates*.—*Method* (*a*). *N*-*p*-Sulphamylphenyl-D-mannosylamine (Bognár and Nánási, *loc. cit.*) (5·0 g.) was kept in pyridine (50 ml.) with acetic anhydride (20 ml.) for 3 days. Evaporation to dryness *in vacuo* and crystallisation from alcohol gave the β-*anomer* (5·3 g., 70%), m. p. 184°, obtained pure by further crystallisation (Found : N, 5·6. $C_{20}H_{26}O_{11}N_2S$ requires N, 5·6%).

Method (*b*). Acetobromomannose (5·0 g., 1·2 mols.) and sulphanilamide (1·7 g., 1 mol.) were treated in acetone (15 ml.) with 10% sodium hydroxide solution (5 ml.). The product was worked up in the usual way. The alcoholic solution yielded a product " A " (0·8 g.), $[\alpha]_D$ −107°. From the mother-liquor a crystalline product " B " (0·45 g.) was obtained, having $[\alpha]_D$ −82°, which was a mixture. Product " A " was purified by repeated crystallisation from methanol, giving the pure β-*anomer* (Found : N, 5·6; Ac, 35·0. $C_{20}H_{26}O_{11}N_2S$ requires N, 5·6; Ac, 34·25%). The methanolic liquor afforded the α-anomer, which was purified from ether–light petroleum.

N-p-*Sulphamylphenyl*-D-*mannosylamine* N : N : 2 : 3 : 4 : 6-*Hexa-acetate*.—The D-mannosylamine 2 : 3 : 4 : 6-tetra-acetate (1·0 g.) with acetic anhydride (10 ml.) and zinc chloride (1 g.) at 100° during 10 min. gave the *hexa-acetate*, m. p. 133—134° (from alcohol), $[\alpha]_D^{22}$ +62·5° (*c*, 1·1 in pyridine), +73·3° (*c*, 0·6 in $CHCl_3$) (Found : N, 4·7; Ac, 44·3. $C_{24}H_{30}O_{13}N_2S$ requires N, 4·8; Ac, 44·0%).

N-p-*Tolyl*-D-*mannosylamine* 2 : 3 : 4 : 6-*Tetra-acetates*.—*Method* (*a*). *N*-*p*-Tolyl-D-mannosylamine (Weygand, *loc. cit.*) in pyridine (50 ml.) with acetic anhydride (20 ml.) at room temperature gave a product (5·7 g.) which, worked up in the usual way and crystallised from alcohol, was a mixture of $[\alpha]_D$ −31·5° in pyridine. After 5 crystallisations from methanol the pure α-isomer

(0·55 g.) was obtained. The material precipitated by water from the mother-liquor was purified as described below, the β-isomer being obtained.

Method (*b*). Acetobromomannose (8·0 g., 1·2 mols.) reacted in the usual way with *p*-toluidine (1·6 g., 1 mol.) in acetone in the presence of sodium hydroxide. Crystallisation from alcohol yielded directly pure deacetylated *N*-*p*-tolyl-D-mannosylamine (0·3 g.), m. p. 180°, $[\alpha]_D$ −176° in pyridine. Addition of water to the mother-liquor gave a product (3·85 g., 50%), $[\alpha]_D$ −40° in pyridine; when this crystallised from ethanol or methanol the crops became gradually

	Method of prep.	α-Anomer		β-Anomer	
		M. p.*	$[\alpha]_D$ (Solvent) *	M. p.*	$[\alpha]_D$ (Solvent) *
D-Glucosylamine tetra-acetate derivatives.					
N-*p*-Tolyl	*a*—*d*	145°	+ 216° (Pyr); + 194·2° ($CHCl_3$) + 228·3 ⟶ +27·8° (HCl–MeOH)	148° (147°,[b]; 144—145°[c]; 141—142°[d])	− 78·0° (Pyr); − 53·7° ⟶ + 25·8° (HCl–MeOH) − 47·2 (− 47·1,[a] − 35·0,[d] − 33·4[e]) ($CHCl_3$)
N-*p*-Bromophenyl	*b*, *d*	150—152	+ 168·0 (Pyr) + 147·0 ⟶ + 33·4 (HCl–MeOH)	162 (157,[a] 160[b])	− 65·0 (Pyr); − 53·0 ⟶ + 31·3 (HCl–MeOH) − 44·7 (− 42·9[e]) ($CHCl_3$)
N-(4-Carboxy-3-hydroxyphenyl)	*b*, *d*	87	+ 107 (Pyr) (? impure)	133—134	− 87·8 (Pyr); − 51·0 ($CHCl_3$)
N-*p*-Sulphamylphenyl	*a*, *b*, *d*	(204—205°)	+ 210·0 ⟶ + 26 (HCl–MeOH) (+ 203°) (Pyr); (+ 197°) ($CHCl_3$)	(204°)	− 44·5 ⟶ + 28° (HCl–MeOH) (− 81°) (Pyr); (− 56·5°) ($CHCl_3$)
N-*p*-Nitrophenyl	*a*	168	+ 206·2 (Pyr) + 229·2 ⟶ + 44·0 (HCl–MeOH)	(180[f])	− 99·2 ⟶ + 38·2 (HCl–MeOH) (− 120[f]) (Pyr)
D-Mannosylamine tetra-acetate derivatives.					
N-*p*-Tolyl	*a*, *b*	168	+ 80·2 (Pyr); + 59·4 ($CHCl_3$) + 111·0° ⟶ − 22·5 (HCl–MeOH)	138	− 153·0 (Pyr); − 87·5 ($CHCl_3$) − 125·0 ⟶ − 18·0 (HCl–MeOH)
N-*p*-Sulphamylphenyl	*a*, *b*	196	+ 48·0° (Pyr) + 77·2 ⟶ 29·0 (HCl–MeOH)	193	− 149·8 (Pyr) − 113·0 ⟶ − 33·1 (HCl–MeOH)
D-Galactosylamine tetra-acetate derivative.					
N-*p*-Tolyl	*a*, *b*, *c*	128	+ 189·1 (Pyr) + 212·0 ⟶ + 43·7 (HCl–MeOH)	127	− 53·0 (Pyr) − 24·9 ⟶ + 43·5 (HCl–MeOH)

* Values in parentheses are from the literature. Mutarotations were complete in 5 min.
[a] Weisz, Diss., Budapest, 1940. [b] Baker, *J.*, 1928, 1583. [c] Honeyman and Tatchell, *J.*, 1950, 967. [d] Ellis and Honeyman, *J.*, 1952, 2053. [e] Bognár and Nánási, *J.*, 1953, 1703. [f] Weygand, *Chem. Ber.*, 1951, **84**, 594.

enriched in the α-*anomer* (Found: N, 3·15; Ac, 40·7. $C_{21}H_{27}O_9N$ requires N, 3·2; Ac, 39·4%); the β-*anomer* (Found: N, 3·3%) was separated from the mother-liquors by addition of water and recrystallised from carbon tetrachloride (0·29 g.).

Method (*c*). *p*-Toluidine (2·0 g., 4 mols.) and penta-*O*-acetyl-D-mannose (2·0 g., 1 mol.) were dissolved in ethanol (20 ml.), and acetic acid (1 ml.) was added. After 2 days the mixture was poured into water, and the solidified crude product (2·0 g.) crystallised from ethanol (20 ml.) (yield, 0·7 g.; $[\alpha]_D^{22}$ −27° in pyridine). The material (1·1 g.) precipitated from the ethanolic mother-liquor by water crystallised from methanol (11 ml.) (yield, 0·7 g.). The products were purified and identified as usual.

N-p-*Tolyl*-D-*galactosylamine* 2 : 3 : 4 : 6-*Tetra-acetates.*—*Method* (*a*). *N*-*p*-Tolyl-D-galactosylamine (5 g.; Ellis and Honeyman, *J.*, 1952, 1496) was treated in pyridine with acetic anhydride. The crude product could not be crystallised from ethanol. From the ether solution a crystalline substance (0·45 g.), m. p. 123°, $[\alpha]_D$ −51° in pyridine, was precipitated on addition of light petroleum; crystallisation from alcohol then afforded the pure β-*anomer* (Found: N, 3·3%).

Method (*b*). *p*-Toluidine (0·8 g.) and acetobromogalactose (4·0 g.) in acetone containing alkali gave only 0·07 g. of pure β-anomer.

Method (*c*). Keeping penta-*O*-acetyl-D-galactose (2·0 g.) and *p*-toluidine (2·2 g.) in absolute ethanol (30 ml.) containing acetic acid (1 ml) for 2 days at room temperature, then pouring the mixture in water, gave a product (1·15 g.), $[\alpha]_D^{22}$ +22° in pyridine. Recrystallisation from 96% alcohol yielded pure β-anomer (0·35 g.).

Preparation of (+)-N-p-*Tolyl-*D-*galactosylamine* 2 : 3 : 4 : 6-*Tetra-acetate from the* (−)-*Isomer.*—(−)-*N-p*-Tolyl-D-galactosylamine tetra-acetate (1·57 g.) was dissolved in methanol (6 ml.), and N-methanolic hydrogen chloride (0·5 ml.) was added. After 10 min. at room temperature the solution was poured into water (50 ml.), and the crude product crystallised from ethanol, giving material (0·64 g.) of $[\alpha]_D$ −37° in pyridine. By treating the mother-liquor with water and by further crystallisation the *α-isomer* (Found: N, 3·1%) was obtained.

(+)-*N-p*-Nitrophenyl-D-glucosylamine 2 : 3 : 4 : 6-tetra-acetate was similarly obtained from the (−)-isomer (prepared by method *a*; cf. Weygand, *Chem. Ber.*, 1951, **84**, 594).

With respect to this and the following two papers we are grateful to Mrs. É. Rákosi, Miss M. Fodor, and Mrs. I. Farkas for the analyses, and to the Hungarian Academy of Science for support.

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Transglycosylation of N-*Arylglycosylamines.*

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N-p-Sulphamylphenyl- and *N-m*- and *N-p*-nitrophenyl-D-glucosylamine have been prepared by the interaction of various *N*-aryl-D-glucosylamines with the appropriate amines. A simple method is described for such transglycosylations, which proved to be reversible in certain circumstances. Mechanisms are discussed.

IN a preliminary report Bognár and Nánási (*Nature*, 1953, **171**, 475) stated that "transglycosylation" of *N*-arylglycosylamines occurs with remarkable ease. The process is now found to be fairly general.

The term "transglycosylation" denotes migration or transfer of the glycosyl part of an *O*-glycosyl or *N*-glycosyl derivative to some other hydroxy- or amino-compound. These reactions are of interest both chemically and biochemically. According to recent investigations some enzymes appear to catalyse such processes. *E.g.*, Kalckar, MacNuff, and Hott-Jorgensen (*Biochem. J.*, 1952, **50**, 397) report that the extract of *Lactobacillus helveticus* contains a *trans-N*-glycosidase which catalytically promotes the reaction, adenine + hypoxanthine deoxyriboside ⟶ hypoxanthine + adenine deoxyriboside; and *Aspergillus orizae* yields a *trans-O*-glycosidase which promotes transfer of the glucosyl group of an *O* : 4-bonded disaccharide to the 6-position of another saccharide, thus converting maltose into a mixture of *iso*maltose and 4- and 6-*O-iso*maltosyl-D-glucose (Pazur and Rench, *J. Biol. Chem.*, 1952, **196**, 265). Reversibility of the reaction has recently been reported for *iso*maltose (Pazur, *Biochim. Biophys. Acta*, 1954, **13**, 158). Among the rare reports of transglycosylation of *O*-glycosides by purely chemical means, Pigman and Laffre (*J. Amer. Chem. Soc.*, 1951, **73**, 4994) prepared *n*-butyl α-D-glucoside from methyl α-D-glucoside by some hours' boiling with butanolic hydrochloric acid (they term the process transglycosidation).

The first example of transglycosylation of *N*-arylglucosylamines was given in 1936 by Kuhn and Dansi (*Ber.*, 1936, **69**, 1745) who in this way prepared *N*-nitroxylyl- from *N-p*-tolyl-D-glucosylamine in less than 10% yield. They reported that the reverse reaction was not realisable. Inonue and Onodera (*J. Agr. Chem. Soc. Japan*, 1947, **22**, 119) describe the preparation of *N-m*- and *N-p*-nitrophenyl-D-glucosylamine from *N-p*-tolyl-D-glucosylamine by the same method. The preparation of *N*-phenyl- from *N-p*-tolyl-D-glucosyl-

amine, likewise reported there, gave " white tabular crystals, m. p. 120—122° " (*Chem. Abs.*, 1951, **45**, 9481), which appears to be at variance with the statement by Honeyman *et al.* (*J.*, 1950, 967) that *N*-phenyl-D-glucosylamine is not crystalline.

Kuhn and Dansi's method consists in refluxing the glycosylamine in more than 100 parts of absolute alcohol for 8 hours with 4·5 mols. of the amine, and separation of the products by chromatography. Apparently no catalyst was used. We now report a study of the conditions and mechanism of the reaction and a simple general preparative method.

The reaction is dependent on pH. Transglycosylation involves proton-catalysis, while in absence of hydrogen ions there is often no reaction; 0·01—0·1 mol. of hydrogen chloride proved to be a reliable catalyst which will effect transglycosylation in 10—20% (by wt.) methanol or ethanol solution of the starting materials at room temperature in a few minutes. No more heating than is necessary for dissolution (maximum, 5 minutes' boiling) is advisable. Transglycosylation is an equilibrium reaction and can be made reversible under certain conditions: for preparative purposes the reverse reaction may require a different solvent or solvent mixture. The yields are generally good but are determined largely by the relative solubilities. Under proper conditions good yields are obtainable even with 1 mol. of amine per mol. of glycosylamine; an excess of up to 0·5 mol. of amine generally suffices to give a tolerable yield from an appropriately chosen solvent or solvent mixture; we never employed more than 1 mol. excess; the excess of amine then does not interfere with isolation of the products, generally remaining in the mother-liquor.

That the reaction is transglycosylation rather than hydrolysis followed by redistributive reglycosylation is shown by the fact that it occurs readily under completely anhydrous conditions with dry hydrogen chloride, such conditions in most cases affording the best yields. A water content not exceeding 5% generally does not influence the rate of reaction or the yield; in special cases presence of water is even advantageous, by leading to a less soluble hydrate or by influencing the solubility in the " mixed " solvent. More than 5% of water is however detrimental. In the presence of water distributive reglycosylation is of course a possible reaction mechanism. Nevertheless the view that hydrolysis is not involved is supported by the observation that *N*-*p*-sulphamylphenyl-D-glucosylamine is formed from *N*-*p*-nitrophenyl-, *N*-*p*-tolyl-, or *N*-(4-carboxy-3-hydroxyphenyl)-D-glucosylamine 5—10 times faster than by reaction of glucose with sulphanilamide in the presence of the appropriate second amine under similar conditions.

Finally, transglycosylation may be extended from glucose to other aldoses and oligosaccharides, and even to *O*-acetyl-*N*-arylglycosylamines (see following paper).

Experimental

N-p-*Sulphamylphenyl*-D-*glucosylamine*.—(i) *From N-phenyl*-D-*glucosylamine*. Sulphanilamide (5·0 g., 1 mol.) was dissolved in warm absolute alcohol (60 ml.) containing hydrogen chloride (0·045 g.), and finely ground, dry *N*-phenyl-D-glucosylamine (7·5 g., 1 mol.) was added. Precipitation began while the solution was still warm and was complete in about 1·5 min. The crystals, when washed with small amounts of absolute ethanol, were pure *N*-*p*-sulphamylphenyl-D-glucosylamine (6·7 g., 69%), m. p. 202—204° (decomp.), $[\alpha]_D^{22}$ −115° (*c*, 1·2 in pyridine), −122° (*c*, 1·2 in H_2O) (Found: N, 8·4; S, 9·7, 9·7. Calc. for $C_{12}H_{18}O_7N_2S$: N, 8·4; S, 9·6%). Kuhn and Birkofer (*Ber.*, 1938, **71**, 621) report m. p. 195° and $[\alpha]_D$ −123° in H_2O.

(ii) *From* N-m-*nitrophenyl*-D-*glucosylamine*. Sulphanilamide (2·5 g., 1·1 mol.) was dissolved in absolute ethanol (50 ml.) containing hydrogen chloride (0·015 g.). *N*-*m*-Nitrophenyl-D-glucosylamine (4·0 g., 1 mol.) was added and the mixture boiled for 2 min. Precipitation began during the boiling and the mixture soon set to a mass of crystals. Filtration and washing yielded pure *N*-*p*-sulphamylphenyl-D-glucosylamine (3·8 g., 85%), m. p. and mixed m. p. 203—204°, $[\alpha]_D^{22}$ −113·2° (*c*, 0·9 in pyridine) (Found: N, 8·4, 8·4; S, 9·8, 9·8%).

A 60% yield was obtained from 96% alcohol containing a small amount of concentrated hydrochloric acid. There was no reaction in absolute alcohol in absence of hydrogen chloride.

More than 0·2 mol. of acid gave inferior yields, and uniform products were not obtained if 0·5 or 2 mols. were used. Yields were best with 0·01—0·1 mol. of acid.

(iii) *From* N-p-*nitrophenyl*-D-*glucosylamine*. (*a*) Sulphanilamide (3·6 g., 1 mol.) was dissolved in absolute ethanol containing concentrated hydrochloric acid (0·3 ml.), and *N*-*p*-nitrophenyl-D-glucosylamine (6·0 g., 1 mol.) was added to the hot solution. It dissolved in a few seconds; after approx. 30 seconds heavy precipitation occurred {6·5 g., 97%; m. p. 202°, $[\alpha]_D^{22}$ −116·2° (*c*, 1·2 in pyridine)}. Recrystallisation from alcohol (1 g. in 10 ml.) yielded the sulphamyl derivative (0·75 g.), m. p. and mixed m. p. 204° (Found: N, 8·3; S, 9·6, 9·7%). Addition of water precipitated 70% of the calculated amount of *p*-nitroaniline from the mother-liquor.

Reaction in 96% ethanol in the presence of concentrated hydrochloric acid gave a 72% yield.

Hydrolysis of the pure product by dilute hydrochloric acid gave 78% of sulphanilamide, m. p. 165°.

(*b*) Sulphanilamide (0·86 g., 1 mol.) was dissolved in water (0·3 ml.) and absolute ethanol (20 ml.) containing 1 drop of concentrated hydrochloric acid. *N*-*p*-Nitrophenyl-D-glucosylamine (1·5 g., 1 mol.) was added to the hot solution, dissolving in a few seconds. The solution was heated on the water-bath. Crystals separated without inoculation within 1·5 min. (yield, 1·4 g., 85%; m. p. 202°).

(*c*) Glucose (0·9 g., 1 mol.) was dissolved in water (0·3 ml.); *p*-nitroaniline (0·7 g., 1 mol.) and sulphanilamide (0·86 g.) were added in absolute ethanol (20 ml.) containing 1 drop of concentrated hydrochloric acid. On the water-bath a clear solution was obtained in a few seconds, but precipitation began only after repeated inoculation after 10 min. and required about 30 min. for completion (yield, 1·25 g., 76%).

(iv) *From* N-p-*bromophenyl*-D-*glucosylamine*. Sulphanilamide (3·6 g., 1 mol.) was dissolved in absolute ethanol (62 ml.) containing hydrogen chloride (0·015 g.). *N*-*p*-Bromophenyl-D-glucosylamine (6·8 g., 1 mol.) was added to the hot solution. Crystallisation began in 30 seconds. The crude product {6·0 g., 84%; m. p. 202° (decomp.), $[\alpha]_D^{18}$ −112·0° (*c*, 1·7 in pyridine)} gave, on recrystallisation from 10 parts of ethanol, a 75—80% yield of the pure sulphamyl derivative, m. p. 204°, containing no bromine (Found: N, 8·3; S, 9·7, 9·8%). Hydrolysis as above gave 80% of sulphanilamide, m. p. 164°.

Reaction in presence of small quantities of concentrated hydrochloric acid gave 75% yields.

(v) *From* N-(4-*carboxy*-3-*hydroxyphenyl*)-D-*glucosylamine*. This glucosylamine (5·0 g., 1 mol.) was added to a hot solution of sulphanilamide (2·5 g., 1 mol.) in 99% methanol (70 ml.) containing concentrated hydrochloric acid (0·3 ml.). The solution became solid in 2 min. {yield, 4·9 g., 92%; m. p. 197°, $[\alpha]_D^{21}$ −112·0° (*c*, 1·2 in pyridine)}. One recrystallisation afforded a pure product, m. p. and mixed m. p. 204° (Found: N, 8·7; S, 9·7, 9·8%), hydrolysed to sulphanilamide (78% yield). In 96% ethanol, with 2 mols. of sulphanilamide and concentrated hydrochloric acid or ammonium chloride as catalyst, this reaction gave 89% or 83% yield, respectively; under these conditions (NH_4Cl) use of 1 mol. of sulphanilamide gave a 71% yield.

Reaction of 1 mol. each of sulphanilamide, 4-aminosalicylic acid, and glucose in 96% ethanol with ammonium chloride as catalyst was much slower. Precipitation began after 5 min. (instead of 1 min.) and required a further 10 min. for completion (instead of a further 1 min.). The quantity and the quality of the product were as in the previous experiment.

The transglycosylation was much slower in absence of a catalyst.

(vi) *From* N-p-*tolyl*-D-*glucosylamine*. (*a*) Sulphanilamide (0·86 g., 1 mol.) was dissolved in absolute ethanol (20 ml.) and water (0·3 ml.); concentrated hydrochloric acid (1 drop) and *N*-*p*-tolyl-D-glucosylamine (1·35 g., 1 mol.) were added to the hot solution. Crystallisation set in from the hot solution after 3 min. and was complete in a further 5—6 min. {yield 0·75 g., 45%; m. p. 202° (decomp.), $[\alpha]_D^{22}$ −116° (*c*, 1·2 in pyridine)} (Found: N, 8·3%). Hydrolysis of the product gave 76% of sulphanilamide, m. p. 164°.

(*b*) Sulphanilamide (1 mol.), D-glucose (1 mol.), and *p*-toluidine (1 mol.) under the same conditions gave a precipitate on the water-bath only after 25 min., in spite of repeated inoculation; crystallisation was complete in about 70 min. The yield was 0·65 g. (40%) of a product, m. p. 202°, $[\alpha]_D^{22}$ −114·2° (*c*, 1·2 in pyridine).

N-p-*Nitrophenyl*-D-*glucosylamine*.—(i) *From* N-*phenyl*-D-*glucosylamine*. To *N*-phenyl-D-glucosylamine (4·0 g., 1 mol.) in a mixture of water (9 ml.) and methanol (24 ml.) was added *p*-nitroaniline (2·2 g., 1 mol.) in hot methanol (12 ml.) containing concentrated hydrochloric acid (0·1 ml.). The whole was boiled for 5 min. Crystallisation began from the cooled solution

immediately upon scratching and was complete in a short time. The drained and washed product (1·88—2·02 g., 40—43%), when hydrolysed by dilute hydrochloric acid, gave 90% of *p*-nitroaniline, m. p. 147°. The glycosylamine was recrystallised from aqueous ethanol and washed with ether; it then had m. p. 184° (decomp.), $[\alpha]_D^{22}$ −193° (*c*, 1·4 in pyridine) (Found: N, 8·3; H_2O, 9·4. Calc. for $C_{12}H_{16}O_7N_2,2H_2O$: N, 8·3; H_2O, 10·7%). Weygand (*loc. cit.*) gives m. p. 184°, $[\alpha]_D^{20}$ −192° (*c*, 1·0 in pyridine).

The reaction also occurs in absolute ethanol in the presence of small amounts of hydrogen chloride, but the product is precipitated much more slowly (ice-cooling is necessary).

(ii) *From* N-o-*nitrophenyl*-D-*glucosylamine*. *N-o*-Nitrophenyl-D-glucosylamine (1·0 g., 1 mol.) and *p*-nitroaniline (0·5 g., 1 mol.) were boiled in methanol (12 ml.) and water (2 ml.) containing concentrated hydrogen chloride (0·05 ml.) for 10 min. and then kept for a day at 0°. The crude precipitate (0·8 g.; N, 8·55%) was recrystallised from ethanol (0·5 g. yielded 0·35 g.; overall yield of pure product 56%). The pure product had m. p. 184°, $[\alpha]_D^{22}$ −198° (*c*, 1·2 in pyridine). Hydrolysis of 0·2 g. as above gave 79% of *p*-nitroaniline, m. p. and mixed m. p. 147—148°.

(iii) *From* N-m-*nitrophenyl*-D-*glucosylamine*. Dry *N-m*-nitrophenyl-D-glucosylamine (4·0 g., 1 mol.) was dissolved in absolute methanol (30 ml.). *p*-Nitroaniline (2·0 g., 1·1 mol.) in warm absolute methanol (20 ml.) was added and then absolute methanol (3 ml.) containing hydrogen chloride (0·066 g.). The mixture was boiled for 5 min. Crystallisation began on cooling. Hydrolysis of the crude product yielded pure *p*-nitroaniline, m. p. 147°. The overall yield of pure glucosylamine, recrystallised from alcohol, was 65%, the product having m. p. 183°, $[\alpha]_D^{22}$ −200° (*c*, 1·2 in pyridine) (Found: N, 9·1. Calc. for $C_{12}H_{16}O_7N_2$: N, 9·3%). Hydrolysis gave 95% of *p*-nitroaniline.

Reaction does not occur in absence of hydrogen chloride. Crystallisation begins at once upon addition of one drop of concentrated hydrochloric acid.

(iv) *From* N-p-*sulphamylphenyl*-D-*glucosylamine*. This glucosylamine (10·0 g., 1 mol.) in hot methanol (60 ml.) and water (20 ml.) was treated with *p*-nitroaniline (8·0 g., 2 mols.) in methanol (40 ml.) containing concentrated hydrochloric acid (0·3 ml.). The mixture was refluxed for 10 min. Crystallisation began immediately on cooling. The crude product {7·7 g., 85%; m. p. 175°, $[\alpha]_D^{22}$ −180° in pyridine} was filtered off after 2 hr. and yielded on hydrolysis *p*-nitroaniline (0·14 g. from 0·4 g.), m. p. 148°. The crude product, when crystallised from absolute ethanol (overall yield 70%), had m. p. and mixed m. p. 182°, $[\alpha]_D^{22}$ −197·8° (Found: N, 9·4%).

(v) *From* N-p-*bromophenyl*-D-*glucosylamine*. This glucosylamine (6·0 g., 1 mol.) was dissolved in methanol (36 ml.) and water (12 ml.). A hot solution of *p*-nitroaniline (3·0 g., 1·15 mol.) in methanol (24 ml.) containing concentrated hydrochloric acid (0·2 ml.) was added. The whole was boiled for 5 min. Crystallisation began immediately upon cooling. The crude product (3·8 g., 67%) crystallised from aqueous ethanol. The pure product contained no bromine and had m. p. and mixed m. p. 181°, $[\alpha]_D^{22}$ −196° (*c*, 1·2 in pyridine) (Found: N, 8·3%). Hydrolysis gave 85% of *p*-nitroaniline.

(vi) *From* N-(4-*carboxy*-3-*hydroxyphenyl*)-D-*glucosylamine*. This amine (5·0 g.) and *p*-nitroaniline (3·0 g., 1·5 mols.) were dissolved in cold methanol (60 ml.). Concentrated hydrochloric acid (0·3 ml.) was added. Crystallisation set in after about 2 min. The crude product (4·8 g., 100%) was fairly uniform, having $[\alpha]_D^{22}$ −186·0° in pyridine (Found: N, 8·4%). Recrystallisation from ethanol and successive washing with water, methanol, and ether gave 75% of the pure product, m. p. and mixed m. p. 181°, $[\alpha]_D^{22}$ −198·5° (*c*, 1·2 in pyridine). Hydrolysis gave results as above.

Reaction does not occur in absence of acid. With 2 mols. of *p*-nitroaniline yields better than 90% were obtained.

N-m-*Nitrophenyl*-D-*glucosylamine*.—(i) *From* N-p-*nitrophenyl*-D-*glucosylamine*. Dry *N-p*-nitrophenyl-D-glucosylamine (4·0 g., 1 mol.) was dissolved in warm ethanol (20 ml.). *m*-Nitroaniline (3·0 g., 1·5 mol.) was added in alcohol (10 ml.) containing hydrogen chloride (0·0035 g.). The mixture was boiled for 5 min. and then cooled. The crystalline precipitate was filtered off and crystallised from absolute alcohol (yield, 60%; hydrolysis gave *m*-nitroaniline, m. p. 114°) and had m. p. and mixed m. p. 177—178°, $[\alpha]_D^{22}$ −167° (*c*, 1·2 in pyridine) (Found: N, 9·5%). Weygand (*loc. cit.*) gives m. p. 178°, $[\alpha]_D^{20}$ −171° in pyridine.

(ii) *From* N-p-*sulphamylphenyl*-D-*glucosylamine*. The sulphamyl derivative (6·0 g., 1 mol.) and *m*-nitroaniline (3·2 g., 1·5 mols.) were dissolved in aqueous ethanol (17 : 3) (30 ml.). Concentrated hydrochloric acid (1 ml.) was added and the whole boiled for 10 min., then kept at 0°. The precipitated product was filtered off, the mother-liquor was concentrated, and the new

crop separated. The precipitates were united and extracted with 6—7 parts of hot methanol; the methanolic extract was concentrated to small volume. The crystals obtained on cooling (1·8 g., 33%; m. p. 174—177°) crystallised from a small amount of ethanol and then had m. p. 176—177° (yield 21%), $[\alpha]_D^{29}$ −166·1° (*c*, 1·2 in pyridine) (Found: N, 9·4%; S, nil.). Hydrolysis gave 83% of *m*-nitroaniline, m. p. 114°.

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Transglycosylation of N-*Aryl-mannosyl-, -galactosyl-, and -lactosyl-amine, and Tetra*-O-*acetyl*-N-*arylglucosylamine.*

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The transglycosylation reaction has been extended to the mannose, galactose, and lactose series, and to a glucosylamine tetra-acetate. It seems to be governed by the relative basicities of the amine components.

IN extension of previous work (preceding paper) on the transglycosylation reaction experiments with D-mannosyl-, D-galactosyl-, and lactosyl-amine, and with D-glucosylamine tetra-acetate are recorded. Conversion of *N*-*p*-sulphamylphenyl-D-glucosylamine tetra-acetate by *p*-bromoaniline into *N*-*p*-bromophenyl-D-glucosylamine tetra-acetate and of the latter tetra-acetate into the former by sulphanilamide proves the reaction be reversible (cf. preceding paper).

A pure anomeric form of any of the *N*-arylglucosylamine tetra-acetates gives an anomeric mixture in warm alcoholic hydrogen chloride, equilibrium being rapidly reached.

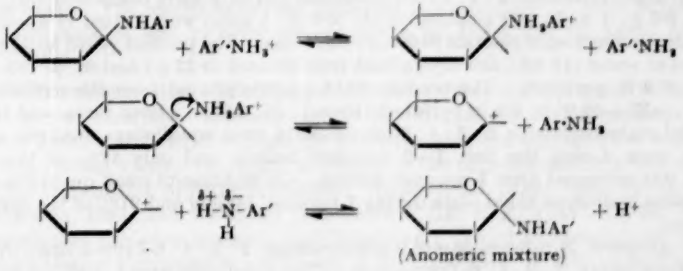
Transglycosylation of the tetra-acetates in anhydrous solvents supports the view that the reaction does not involve hydrolysis, and this is confirmed by the following facts: (*a*) (*a*) D-Glucose tetra-acetate does not react, at least not to a practicable extent, under the usual conditions of the reaction. (*b*) In the absence of another amine the acetylated glycosylamines mutarotate, under the conditions of transglycosylation, to equilibrium within 2 minutes, and the anomeric mixtures can be isolated in 50—60% yields. Further heating causes strong coloration and a reaction which has not been explained. However, if a proton-acceptor, *e.g.*, pyridine, is added, no coloration occurs and after 6—8 minutes' heating a yield exceeding 90% of the anomeric mixture is recovered, so the hydrolysis, if any, is very slight.

The less basic amines are best suited to transglycosylation, since the proton-affinity of the stronger amine will govern the reaction.

The pure anomeric tetra-acetates separated from the mixture obtained by transglycosylation correspond to those prepared as described in the preceding paper.

This represents a new method for preparation of *O*-acetylglycosylamines and further supports the pyranoside structure of these compounds.

The results suggest a proton-catalysed mechanism for transglycosylation (see annexed scheme).



Experimental

N-p-*Tolyl*-D-*mannosylamine from* N-p-*Sulphamylphenyl*-D-*mannosylamine*.—*N*-*p*-Sulphamylphenyl-D-mannosylamine (1·0 g., 1 mol.) and *p*-toluidine (0·5 g., 1·3 mols.) were boiled in methanol (8 ml.) and water (4 ml.) containing 3 drops of concentrated hydrochloric acid. Dissolution took place after 15 min. Crystallisation set in at room temperature, yielding 0·7 g. (87%) of crude product. Recrystallised twice from aqueous methanol (yield, 70%) this had m. p. 182° alone or mixed with *N*-*p*-tolylmannosylamine, $[\alpha]_D^{22}$ −178° (*c* 0·9 in pyridine), −99·1° (*c*, 1·0 in MeOH) (Found: C, 57·4, 57·2; H, 6·9, 6·7; N, 5·4. Calc. for $C_{13}H_{19}O_5N$: C, 58·0; H, 7·1; N, 5·2%). Weygand (*Ber.*, 1939, **72**, 1663) gives m. p. 183—184°; Ellis and Honeyman (*J.*, 1952, 1496) give $[\alpha]_D^{22}$ −181° in pyridine.

N-p-*Sulphamylphenyl*-D-*galactosylamine from* N-(4-*Carboxy*-3-*hydroxyphenyl*)-D-*galactosylamine*.—*N*-(4-Carboxy-3-hydroxyphenyl)-D-galactosylamine (0·7 g., 1 mol.) and sulphanilamide (0·4 g., 1·05 mols.) were boiled for 5 min. in 80% methanol containing 0·004 g. of hydrogen chloride. Ether was added to the cooled solution. The precipitated product crystallised from aqueous ethanol (yield 50%) and had m. p. 174° alone or mixed with *N*-*p*-sulphamylphenylgalactosylamine, $[\alpha]_D$ −95° (*c*, 1·5 in pyridine) (Found: N, 7·8; S, 9·2, 9·3. Calc. for $C_{18}H_{16}O_7N_2S,H_2O$: N, 8·0; S, 9·1%). Bognár and Nánási (*J.*, 1953, 1703) gave m. p. 174—175°, $[\alpha]_D$ −97° in pyridine. Hydrolysis of 0·3 g. by acid gave 0·145 g. of sulphanilamide, m. p. 164°.

N-p-*Sulphamylphenyl-lactosylamine from* N-(4-*Carboxy*-3-*hydroxyphenyl*)-*lactosylamine*.—*N*-(4-Carboxy-3-hydroxyphenyl)-lactosylamine (1·6 g., 1 mol.) and sulphanilamide (0·6 g., 1·05 mols.) were boiled for 5 min. in 70% ethanol (12 ml.) containing hydrogen chloride (0·007 g.). The crude product (1·4 g., 85%) was precipitated from the cooled solution by ether and, crystallised from 83% alcohol (yield 55%), had m. p. 208° alone or mixed with *N*-*p*-sulphamylphenyllactosylamine trihydrate (m. p. 210°), $[\alpha]_D^{22}$ −66·1° (*c*, 1·5 in pyridine) (Found: N, 5·0. Calc. for $C_{18}H_{28}O_{12}N_2S,3H_2O$: N, 5·1%). Bognár and Nánási (*loc. cit.*) give m. p. 210—212°, $[\alpha]_D^{22}$ −69·0° (*c*, 1·7 in pyridine).

Anomeric Mixture of N-p-*Sulphamylphenyl*-D-*glucosylamine Tetra-acetates*.—(a) *From* α-N-*phenyl*-D-*glucosylamine* 2 : 3 : 4 : 6-*tetra-acetate*. *N*-Phenyl-D-glucosylamine 2 : 3 : 4 : 6-tetra-acetate ($[\alpha]$ +150° in $CHCl_3$; 2·1 g., 1 mol.) and sulphanilamide (0·9 g., 1 mol.) were boiled for 15 min. in absolute ethanol (15 ml.) containing concentrated hydrochloric acid (0·05 ml.). The crude product separating on cooling {0·72 g., 64%; m. p. 185°, $[\alpha]_D^{22}$ +60·0° (*c*, 1·0 in pyridine)} crystallised from ethanol and then had m. p. 188—192°, $[\alpha]_D^{24}$ +95·0° (*c*, 0·9 in pyridine), being a mixture of the anomeric *N*-*p*-sulphamylphenyl-D-glucosylamine 2 : 3 : 4 : 6-tetra-acetates.

Similar reaction in 96% ethanol gave a 70% yield of a mixture, m. p. 190°, $[\alpha]_D^{22}$ +26·2° (*c*, 0·7 in pyridine) (Found: N, 5·6. Calc. for $C_{20}H_{26}O_{11}N_2S$: N, 5·6%), which contains more of the lævorotatory anomer. This product yielded, with acetic anhydride and zinc chloride (Bognár and Nánási, *loc. cit.*), the hexa-acetate, m. p. 115°, $[\alpha]_D$ +75° (*c*, 0·7 in pyridine). Bognár and Nánási give m. p. 115°, $[\alpha]$ +77°.

(b) *From* β-N-*phenyl*-D-*glucosylamine* 2 : 3 : 4 : 6-*tetra-acetate*. The dry tetra-acetate ($[\alpha]_D$ −37° in $CHCl_3$; 1·0 g., 1 mol.) and sulphanilamide (0·43 g., 1 mol.) were boiled for 15 min. in absolute ethanol containing hydrogen chloride (0·007 g.). The crude product, recrystallised from alcohol, gave a mixture of anomers (yield 60%), m. p. 185°, $[\alpha]_D^{22}$ +49·4° (*c*, 0·6 in pyridine) (Found: N, 5·4%).

Anomeric Mixture of N-p-*Sulphamylphenyl*-D-*glucosylamine* 2 : 3 : 4 : 6-*Tetra-acetates from* β-N-p-*Tolyl*-D-*glucosylamine* 2 : 3 : 4 : 6-*Tetra-acetate*.—The *p*-tolyl compound ($[\alpha]_D$ −58·5° in pyridine; 0·5 g., 1 mol.) and sulphanilamide (0·2 g., 1 mol.) were heated in absolute ethanol (2 ml.) containing hydrogen chloride (0·004 g.) for 7 min. The product (yield 80%) precipitated on addition of water (10 ml.) and crystallised from ethanol (0·22 g.) had m. p. 185—192°, $[\alpha]_D^{22}$ −30·0° (*c*, 0·9 in pyridine). The product (0·15 g.) precipitated from the mother-liquor had m. p. 180°, $[\alpha]_D^{22}$ +58·0° (*c*, 0·9 in pyridine) (Found: N, 5·6%). Both the α- and the β-isomer of *N*-*p*-tolyl-D-glucosylamine 2 : 3 : 4 : 6-tetra-acetate gave equilibrium mixtures under these conditions, even during the first 1—2 minutes' boiling, and only 47% of the unchanged compound was recovered after 7 minutes' boiling. On addition of small quantities of pyridine no appreciable hydrolysis takes place during 7 minutes' boiling and 91% of the compound can be recovered.

Mixed Anomeric N-p-*Bromophenyl*-D-*glucosylamine* 2 : 3 : 4 : 6-*Tetra-acetates from* β-N-p-*Tolyl*-D-*glucosylamine* 2 : 3 : 4 : 6-*Tetra-acetate*.—The tolyl compound ($[\alpha]_D$ −48°; 0·5 g.,

1 mol.) and *p*-bromoaniline (0·4 g., 2 mols.) were boiled in absolute ethanol (2 ml.) containing hydrogen chloride (0·004 g.) for 5 min. then cooled and diluted with water (10 ml.). A crude oil separated which was twice crystallised from ethanol. The product (0·3 g.) separating from the solution had m. p. 158° alone or mixed with the pure β-anomer and $[\alpha]_D^{22}$ −68° (*c*, 0·9 in pyridine). The mother-liquor, on addition of water, afforded a substance (0·1 g.), m. p. 123°, $[\alpha]_D^{22}$ +86° (*c*, 0·9 in pyridine), +45° (*c*, 1·1 in $CHCl_3$) (Found: N, 2·9. Calc. for $C_{20}H_{24}O_9NBr$: N, 2·8%). Bognár and Nánási (*J.*, 1954, 189) give m. p. 150—152°, $[\alpha]_D$ +168° in pyridine and m. p. 162°, $[\alpha]_D$ −65° for the anomers. The yield of recrystallised products amounts to 50%.

N-p-*Bromophenyl*-D-*glucosylamine* 2 : 3 : 4 : 6-*Tetra-acetate*.—(a) *From* β-N-p-*sulphamylphenyl*-D-*glucosylamine* 2 : 3 : 4 : 6-*tetra-acetate*. The sulphamyl compound ($[\alpha]_D$ −54°; 0·5 g., 1 mol.) and *p*-bromoaniline (0·4 g., 2·15 mols.) were dissolved in hot absolute ethanol (2 ml.) containing hydrogen chloride (0·004 g.). The mixture was boiled for 5 min. after complete dissolution and then cooled. The amorphous product separating on addition of water (10 ml.) crystallised from ethanol (yield 0·3 g.), then having m. p. 161°, $[\alpha]_D^{22}$ −56·5° (*c*, 0·9 in pyridine), −31·6° (*c*, 0·7 in $CHCl_3$). A mixture with the pure dextrorotatory compound melted at 161—162°. The yield of recrystallised product is 60% (Found: N, 3·2%).

(b) *From* α-N-p-*sulphamylphenyl*-D-*glucosylamine* 2 : 3 : 4 : 6-*tetra-acetate*. This anomer, $[\alpha]_D$ +155°, gave similar results in methanol (yield, 0·3 g., 60%; m. p. and mixed m. p. 162°, $[\alpha]_D^{22}$ −56·5° in pyridine) (Found: N, 2·9%).

Both the α- and the β-sulphamyl compound are equilibrated under the conditions of transglycosylation, and after 7 minutes' boiling only 58% of unchanged compound was recovered. On addition of small amounts of pyridine 89% was recovered after 7 minutes' boiling.

N-p-*Sulphamylglucosylamine* 2 : 3 : 4 : 6-*Tetra-acetate from* N-p-*Bromophenyl*-D-*glucosylamine* 2 : 3 : 4 : 6-*Tetra-acetate*.—The bromo-compound, $[\alpha]_D$ −42° (1 mol.) and sulphanilamide (2·15 mols.) in absolute ethanol containing a small amount of hydrogen chloride gave a mixture of anomers (recrystallised from ethanol), m. p. 184—190°, $[\alpha]_D^{23}$ −35·0° (*c*, 0·9 in pyridine) (Found: N, 5·5%). A different mixture was isolated from the mother-liquor; this had $[\alpha]_D^{22}$ +48·8° (*c*, 0·9 in pyridine). The yield of recrystallised products was 60%.

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Effect of Solid Surfaces on the Propagation of Flame through Ethylene–Air Mixtures.

By M. F. HOARE and J. W. LINNETT.

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Three types of experiment have been carried out to investigate the effect of solid surfaces on the propagation of flame through various ethylene–air mixtures. These are: (*A*) Measurements of minimum tube diameters for flame propagation. (*B*) Measurements of critical flow rates for flash-back down cylindrical burner tubes; from these critical velocity gradients at the wall and penetration distances have been calculated. (*C*) Observations of the products of combustion after explosion in a small combustion chamber; from the results it was concluded that a portion near the wall was not consumed by the flame. The results have been discussed separately and in relation both to one another and to some measurements by Holm and by Lewis and von Elbe.

THERE is much evidence that the ability of a flame to propagate is considerably affected by the presence of a surface. For instance, it has been found that a mixture which will carry a flame down a wide tube will not do so down tubes the diameters of which are less than a certain critical value; *i.e.*, when all points in the tube are within a certain distance of the wall no propagation of flame is possible. Holm (*Phil. Mag.*, 1932, **14**, 18; 1933, **15**, 329) and Garside, Hall, and Townend (*Trans. Inst. Gas Eng.*, 1941—42, **91**, 80), among others, investigated this phenomenon; and Friedman ("Third Symposium on Combustion Flame and Explosion Phenomena," Williams & Wilkins, 1949, p. 110) and others (Harris,

Grumer, von Elbe, and Lewis, *ibid.*, p. 80) have studied the similar limiting separation for propagation of flame in a space bounded by plane surfaces. Another effect that can be used to obtain information about the effect of adjacent surfaces is that of " strike-back " or " flash-back " in a burner. This has been treated theoretically by Lewis and von Elbe who deduce from the results a quantity which they call the " penetration distance " (" Combustion, Flames, and Explosion of Gases," Academic Press, 1951, p. 285; cf. Wohl, Kapp, and Gazley, " Third Symposium, etc.," *op. cit.*, p. 3), which, in their treatment, measures the distance from the surface to the point where the burning velocity is equal to that in free space, it being supposed that it is lower in the region near the surface than it is in free space. Similar ideas have also been put forward by Forsyth, Davies, and Townend (*Trans. Inst. Gas Eng.*, 1941—42, **91**, 47; see also, Garside, Forsyth, and Townend, *J. Inst. Fuel*, 1944—45, **18**, 175, and Forsyth and Garside, " Third Symposium, etc.", *op. cit.*, p. 99). These authors relate the distances between the base of the visible inner cone and the top of the burner tube, which they call the " dead space," with the distance to which a surface can affect flame propagation (*i.e.*, Lewis and von Elbe's " penetration distance "). Whether this is justified seems uncertain. A flame cannot be treated as a single surface, and light emission is late in the succession of events constituting a flame, as is shown, for instance, by the separation between the visible and Schlieren shadow cones (van de Poll and Westerdijk, *Z. tech. Physik*, 1941, **22**, 29). This " dead space " above the burner port is not observed if Schlieren shadow photography is used.

In the present paper some results that have been obtained for ethylene–air mixtures are presented. They are of three types: (*A*) Measurements of minimum tube diameters for flame propagation for a range of mixtures; (*B*) measurements of limiting flow rates for flash-back down cylindrical tubes; (*C*) observations of the products of combustion of ethylene–air mixtures after explosion in a small combustion chamber. These will be described and discussed separately in three sections, and a general discussion is given at the end.

Section *A*

Experimental.—The apparatus used is shown in Fig. 1. The volume above the mercury in *F* was filled with a known mixture by drawing it in from a flow line, the mixture having been made up by adjusting calibrated flow-meters. The ethylene was prepared by dehydrating ethyl alcohol with metaphosphoric acid, and the air was obtained from the compressed-air supply. The gas was forced out of *F* into *G* and through the test capillary *H*, the diameter of which had been obtained by weighing a mercury pellet of measured length. A flame was lit and then the flow stopped to see whether the flame would travel back down the tube or not. A side tube from *G* dipping into mercury acted as a safety valve when inflammation reached *G*, and a gauze sealed into *G* eliminated the danger of the flame's passing into *F*.

Results.—Six tubes were tested, and the limits of ethylene content in which they allowed passage of flame were as follows:

Radius of tube, mm.	0·880	0·948	0·968	1·033	1·126	1·197
Limits of C_2H_4 (%)	(None)	7·0—8·15	6·65—8·40	6·0—8·65	5·55—9·0	5·1—9·5

These results agree well with those given by Garside, Hall, and Townend (*loc. cit.*). This is interesting, for the present results were obtained by using glass tubes, whereas their experiments were carried out with holes in metal plates only 0·43 mm. thick.

Discussion.—The results are shown graphically in Fig. 2, from which it will be seen that the minimum tube radius must be about 0·93 or 0·94 mm. for a mixture containing about 7⅞% of ethylene, which is the mixture having the maximum burning velocity as determined by the burner method (Schlieren) (Conan and Linnett, *Trans. Faraday Soc.*, 1951, **47**, 981) and the soap-bubble method (Pickering and Linnett, *ibid.*, p. 989). However, there is no simple relation between the burning velocity and limiting diameter. For instance for mixtures containing both 5 and 9·5% of ethylene the limiting radius is 1·22 mm., but the burning velocity for the former mixture is 43·5 cm./sec. as against 48 for the latter. Also the burning velocities of mixtures containing 6 and 9% of ethylene are both 56 cm./sec.; yet the limiting radius for the former mixture is 1·03 mm. and for

the latter 1·12 mm. That is, for mixtures having the same burning velocity the rich mixture requires wider tubes for propagation than does the lean mixture.

Section *B*

Experimental.—The ethylene and air flow-rates were measured on capillary flow-meters. The gases were mixed and passed up the cylindrical tube in which the flash-back limits were to be determined. Three tubes were used : two of glass of internal radii 0·398 and 0·484 cm., and one of steel of internal radius 0·494 cm. The procedure for determining the critical volume flow rate for flash-back for a known mixture in a given tube was as follows : A mixture was first passed through the tube at such a flow rate that it would produce a stable flame. The flow rate of the air was reduced until the flow rate and composition had changed to those of a mixture which just struck back. The flow rate was then made just a little greater than that for strike-back, and the flow rate of air again reduced. The flow rates of both gases at strike-back were again noted, and the process repeated. It was possible to fix the limiting flow rate for strike-back for a given mixture with an accuracy of ± 1 c.c./sec. in a total flow rate of the order of 100 c.c./sec.

Results.—The results are presented in terms of the critical velocity gradient in sec.$^{-1}$ at the wall when flash-back occurs. The velocity gradient at the wall in a tube of radius R in which

Fig. 1. *Apparatus for determining limiting tube radii for flame propagation.*

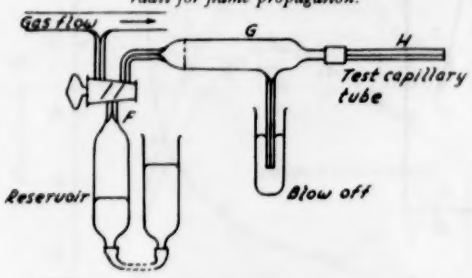
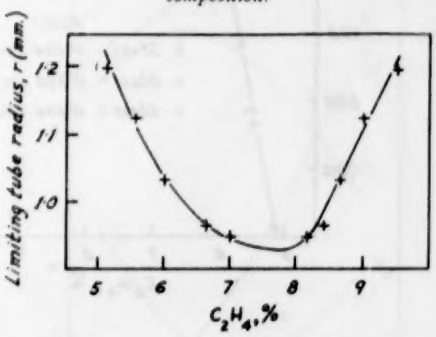


Fig. 2. *Variation of limiting tube radii with composition.*



the volume flow rate is V is $4V/\pi R^3$. This will be called v_g. The graph of the limiting value of v_g, which will be called v_g', against the percentage of ethylene is shown for all three tubes in Fig. 3. It will be seen that v_g' is dependent only on the composition of the mixture and that it is a maximum for a mixture containing about 7$\frac{3}{4}$% of ethylene, which is the mixture having the maximum burning velocity. These results are consistent with those presented by Forsyth, Davies, and Townend (*loc. cit.*), whose experiments were carried out below atmospheric pressure and are given for a single burner tube.

Discussion.—In a tube through which gas is flowing in a stream-lined manner the linear flow rate is zero at the wall. Therefore, near the wall, the flow rate is always less than the burning velocity in free space. This led Lewis and von Elbe to suppose that the burning velocity was reduced by the presence of a nearby surface so that, when a stable flame was burning at the mouth of a cylindrical tube, the flow rate at any point exceeded the effective burning velocity there. When flash-back occurred, they supposed that the effective burning velocity exceeded the flow rate at some point. By following up this idea they were able to show that it was reasonable to suppose that the surface reduced the burning velocity below the value it had in free space (*i.e.*, affected the flame propagation to some extent) to a distance equal to V_b/v_g' from the surface, where V_b is the burning velocity. The values obtained for this quantity for different ethylene percentages (see Fig. 4) were : 5%, 0·78 mm.; 5$\frac{1}{2}$%, 0·63 mm.; 6%, 0·53 mm.; 7%, 0·46 mm.; 8%, 0·46 mm.; 9%, 0·49 mm.; 10%, 0·51 mm. The minimum penetration distance, as the above quantity is called, is about 0·46 mm. for a mixture containing about 7$\frac{1}{2}$% of ethylene. The curve is

very flat near the minimum, so it is difficult to place accurately the percentage at which the minimum lies.

Two facts may be noted about Fig. 4 in relation to the results of Section *A*. (i) For two mixtures having the same burning velocity, the penetration distance is less for the rich

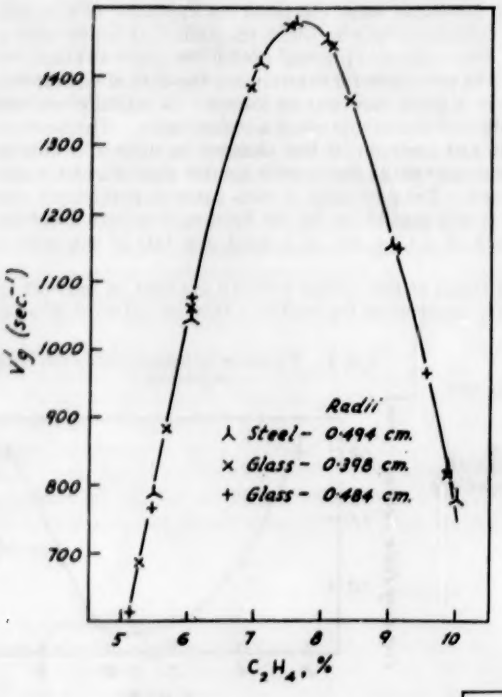


FIG. 3. *Variation of limiting velocity gradient at the wall (v_g') with composition for three different tubes.*

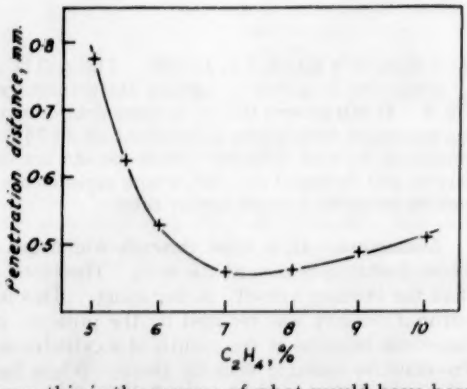


FIG. 4. *Variation of penetration distance with composition.*

mixture than for the corresponding lean one; this is the reverse of what would have been expected from Section *A*, for there it was found that, for two mixtures having the same burning velocity, the lean one could propagate flame in a tube the radius of which was less than the critical value for the rich one. (ii) The penetration distances of this section are less than the minimum radii of Section *A*. Since the penetration distance measures the distance to which some effect of the wall is experienced by the flame, whereas, in Section *A*, measurements were made of the tube radii necessary to extinguish the flame completely, this is perhaps surprising. The result is probably due, in part, to the fact that the

curvatures of the surfaces were greater in Section *A* than those used in the experiments described in this section. In the experiments of this section the radii of curvature of the surfaces were large compared with the penetration distances. It may also be due, in part, to the fact that the flame that travels down the narrowest tube possible must have itself a finite diameter and yet cannot approach too closely to the wall. A similar view has been expressed by Garside, Forsyth, and Townend (*loc. cit.*), who say, " the opinion has been formed that the limiting diameter in any particular case approximates to twice the dead space plus an allowance for the actual passage of the flame."

Section *C*

Experimental.—Various mixtures of ethylene and air of known composition were enclosed in a tube of radius 5 mm. over mercury and ignited by means of a spark. The volume of the

FIG. 5. *Observed variation of the percentage composition of the products with the initial percentage of ethylene.*

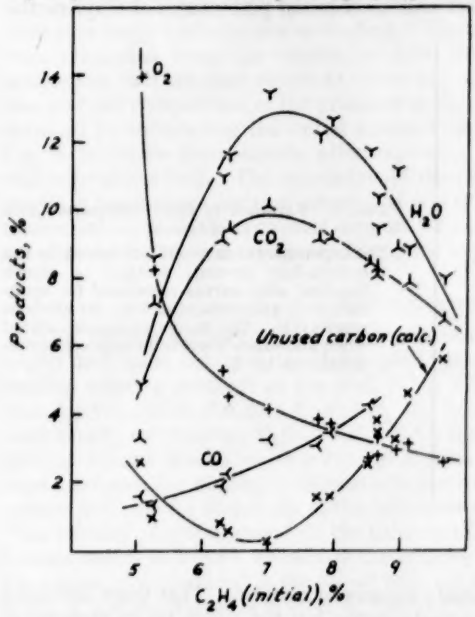
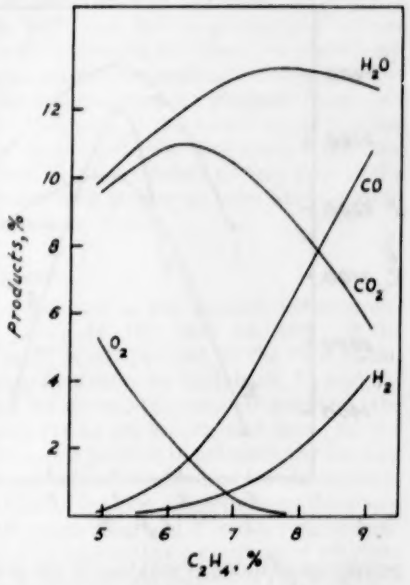


FIG. 6. *Calculated variation of the percentage composition of the products with the initial percentage of ethylene.*



mixture had been measured before ignition and the volume remaining was also measured. Both these measurements were made at room temperature and at the same humidity. The volumes of carbon dioxide and oxygen in the mixtures resulting from the explosions were measured by absorbing the former in potassium hydroxide and the latter in alkaline pyrogallol.

It was presumed that the combustion of the ethylene could be represented by :

$$\tfrac{1}{2}(x + y)C_2H_4 + \tfrac{1}{2}(3x + 2y)O_2 = xCO_2 + yCO + (x + y)H_2O$$

where x and y represent volumes to be determined. The contraction on explosion, $\frac{1}{2}(2x + y)$, was measured as well as the volume, x, of carbon dioxide; so y could be deduced. In this it is assumed that all the hydrogen goes to water. This is a reasonable assumption for lean mixtures but is less good for rich ones, so our conclusions regarding the composition of the gases will be more satisfactory for lean than for rich mixtures.

Results.—The results are presented in Fig. 5. The percentages of carbon dioxide and monoxide in the products were determined as above (the percentages plotted in Fig. 5 are those that would be formed if the water remained gaseous—they can be readily calculated from those measured by assuming the above equation to be true). The percentage of water formed was deduced from the values of x and y which were measured. The percentage of oxygen remaining

was determined. The value calculated for this from x and y was found to be in good agreement with that observed. The amount of residual ethylene was calculated on the assumption that all that was consumed went to form the carbon dioxide and monoxide which had been determined. The experimental results in Fig. 5 may be compared with those in Fig. 6 calculated on the assumption that the products existed in equilibrium at an equilibrium flame temperature. The calculated and experimental curves for water, carbon dioxide, and oxygen agree in general form with one another, though the experimentally observed changes in the percentages with initial composition are greater than those calculated (*e.g.*, the maxima are sharper). The experimental curve for carbon monoxide is similar to the theoretical one from 5 to 7% but beyond this the percentage of carbon monoxide inexplicably decreases somewhat (points not shown). There is no theoretical curve for unburnt ethylene, for, by assuming equilibrium among the products, it is, as a consequence, assumed that all the ethylene is consumed.

Discussion.—The percentage of unburnt ethylene is a minimum for a mixture containing initially 7% of ethylene, which is the one having the highest calculated and the highest observed flame temperature. At both higher and lower initial percentages of ethylene the

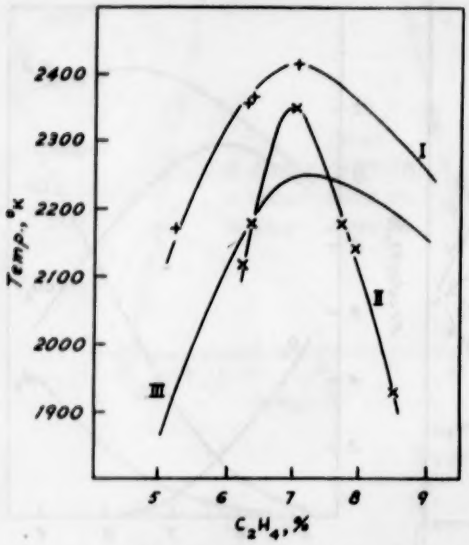


FIG. 7. *Variation of flame temperature with composition.*

The experimental curve (III) obtained by the sodium-line reversal method is shown together with curves calculated for equilibrium (I) and calculated from the analysis results (II). The temperatures calculated when allowance is made for edge correction are shown by +.

percentage of unburnt ethylene in the products appears to increase. That there should be unburnt ethylene in the rich mixtures is understandable, but the reason for its presence in the lean mixtures is not so obvious: the most reasonable explanation of this (and for part of the unburnt ethylene in the products from rich mixtures) is that there is a region near the wall which is not reached by the flame and that, in this space, the ethylene remains unburnt. This would explain why the percentage of unburnt ethylene is a minimum for the hottest flame.

Let us suppose that there is a region near the wall in which the ethylene is not burnt at all, while in the rest of the vessel it is all burnt. Knowing the amount of ethylene present originally, it is possible, from the calculated amount of ethylene remaining unburnt, to deduce the proportion of the volume of the combustion chamber which is unaffected by the passage of the flame. Since the sides of the tube account for the majority of the surface area (the diameter being much less than the length) this proportion may be put equal to $2\pi r.\Delta r/\pi r^2 = 2\Delta r/r$, where r is the radius of the tube (5 mm.) and Δr is the distance from the wall to which the flame is supposed to be quenched. For the experiment with 6·97% of ethylene, Δr was calculated to be 0·09 mm.; for 6·37%, 0·23 mm.; for 6·28%, 0·33 mm.; for 5·24%, 0·48 mm.; and for 5·01%, 1·2 mm. The last figure is probably abnormally large, for the results in Fig. 5 indicate that, in this case, there was a particularly incomplete

combustion compared with those for higher ethylene percentages. The figure for 5·01% of ethylene being omitted, therefore, it will be seen that the values of Δr are less than the corresponding values for the quenching radius and penetration distance. This is not surprising, for it would be expected that after-burning, following the passage of the flame, would consume gas near the wall which had not been burnt during the actual passage of the flame. The ratio of r to the penetration distance varies from one-half to one-fifth on passing from 5 to 7% of ethylene.

Before concluding this section some calculations of the flame temperatures will be presented. In Fig. 7 are shown the flame temperatures calculated by assuming the products to be at equilibrium, and also the flame temperatures observed by the sodium-line reversal method (Jones, Lewis, Friauf, and Perrott, *J. Amer. Chem. Soc.*, 1931, **53**, 869). The third curve is a flame-temperature curve calculated from the analysis results presented in Fig. 5. This was calculated from a knowledge of the heat liberated on going from the initial mixtures to the product mixtures and also the heat capacities of the various substances. This curve was obtained by considering the overall composition of the product mixture, no allowance being made for any wall effect. The four points marked by crosses (+) in Fig. 7 were calculated from the results for 5·24, 6·28, 6·37, and 6·97% of ethylene on the assumption that the part within Δr of the wall was unaffected by the flame (see above) and also that the composition of the products in the remainder of the combustion tube could be obtained by subtracting the initial contents of this volume from the products found (see Fig. 5) to obtain the contents, after explosion, of that part of the vessel which was not within Δr of the wall. The calculation of the final temperature was then made from these results in the manner outlined above. It will be seen that these points lie very close to the theoretical curve. This provides support for the simplified picture we have formulated of the effect of the walls on the gases during the explosion.

General Discussion

Two further matters will be discussed here. The first is the relation between our results and some obtained by Holm (*Phil. Mag.*, 1932, **14**, 18; 1933, **15**, 329). If the limiting velocity gradient at the wall ($v_g' = 4V'/\pi R^3$) is independent of the tube radius then, for two tubes of radius R_1 and R_2, the limiting flow rates for flash-back, V_1 and V_2, must satisfy the relation $V_1/V_2 = R_1^3/R_2^3$. Since, for several ethylene–air mixtures, the limiting volume flow rates for a tube of a particular radius are known, and since, for the same mixtures, the limiting tube radius is also known, it is possible to calculate the limiting volume flow rate for flash-back in the tube of limiting radius. Holm used this to calculate " the velocity of propagation " of the flame in the tube of limiting diameter from the above formula and $v_f = V/\pi R^2$, where v_f is the velocity of propagation and V is the volume flow. The values of v_f, deduced in the above way, are plotted against the percentage of ethylene in Fig. 8, and the values of v_f for 5, 6, 7, 8, and 9% of ethylene are plotted in Fig. 9 against the limiting tube radii for these mixtures, together with some results obtained for other mixtures by Holm. It will be seen that, despite the variety of substances studied, most of the points lie close to a straight line, showing an unexpected regularity in behaviour. This, in effect, suggests that there is a smooth relationship between the critical velocity gradient for flash-back and the limiting tube radius for flame propagation which is independent of the combustible mixture, the relation being such that, as one becomes bigger the other becomes smaller.

A further point arises out of one already mentioned. In Section *B* it was pointed out that the limiting tube diameter could be regarded as being made up of two parts: (*a*) a flame diameter which was the minimum for which flame could propagate, and (*b*) the space between this and the wall in which the flame could not affect the gas because of the quenching effect of the wall. The fact that twice the penetration distance, as determined from the critical velocity gradient for flash back, was always less than the minimum tube diameter supports this concept.

Now, for various methane–oxygen–nitrogen mixtures, Lewis and von Elbe (*loc. cit.*, pp. 418, 426) have recorded the minimum tube diameter (d_0) and minimum distance

between parallel plates ($d_{||}$) for flame propagation. They have also recorded the penetration distances (d_p) calculated from the critical velocity gradients and, in addition, have calculated from minimum energies for spark ignition values for the diameter (d_f) of the smallest sphere of flame that will carry inflammation into the next layer. Values for these quantities, as given by Lewis and von Elbe, are listed in the following Table. In addition, two columns list the values of $\frac{1}{2}(d_0 - d_f)$ and $\frac{1}{2}(d_{||} - d_f)$. These figures may be compared with d_p, the penetration distance, for they may be regarded as measuring the distance within which the quenching effect of the walls is operative. It will be seen that, in most cases, d_p lies between $\frac{1}{2}(d_0 - d_f)$ and $\frac{1}{2}(d_{||} - d_f)$, which is reasonable, for the radius of curvature of the surface used when measuring d_p must have been intermediate between

FIG. 8. *Variation of the calculated velocity of flame propagation in tubes of the limiting radius with composition.*

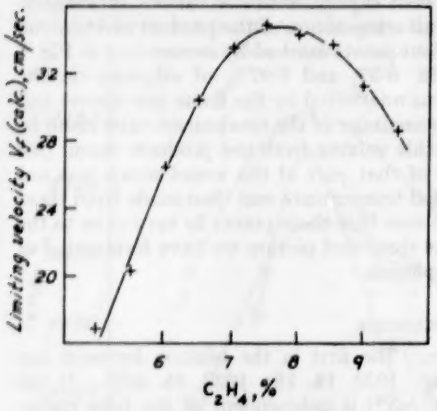
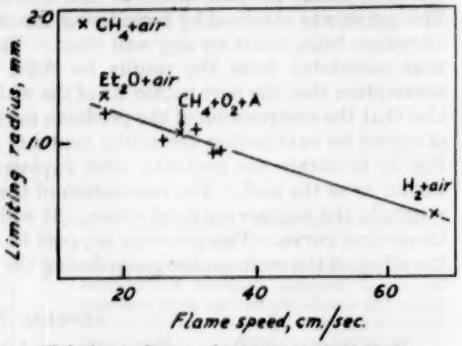


FIG. 9. *Variation of the limiting radius with the limiting velocity of flame propagation.*



Holm's results are shown as ×, ours as +.

the radius of the surface of the tube ($d_0/2$) and that of the plane surface (∞). Moreover, except in one case for which d_f appears to be abnormally large, when it is outside the limits it is only just outside. The general idea of a small flame going down the centre of the tube cushioned from the wall by an annular ring of gas seems to be satisfactory. The results in the Table moreover lend support to the values of d_f calculated by Lewis and von Elbe.

Lewis and von Elbe's values for minimum tube diameters (d_0), *minimum separation between plates* ($d_{||}$), *minimum flame diameters* (d_f), *and penetration distances* (d_p)—*in mm.—for methane–oxygen–nitrogen mixtures.*

Percentages of:								
CH_4	O_2	N_2	d_0	$d_{||}$	d_f	d_p	$\frac{1}{2}(d_0 - d_f)$	$\frac{1}{2}(d_{||} - d_f)$
10	90	—	1·18	0·86	0·38	0·40	0·40	0·24
15	85	—	0·68	0·46	0·17	0·14	0·26	0·15
25	75	—	0·48	0·28	0·16	0·066	0·16	0·06
40	60	—	0·69	0·43	0·32	0·11	0·19	0·06
50	50	—	2·15	1·5	1·06	0·41	0·55	0·22
52·5	47·5	—	3·25	2·2	1·92	1·0	0·67	0·14
10	18·8	71·2	3·35	2·8	0·90	0·90	1·23	0·95
16·3	29·3	54·4	1·42	0·79	0·35	0·44	0·54	0·22
21·5	39·8	39·7	0·92	0·53	0·31	0·19	0·31	0·11
26·4	49·1	24·5	0·70	0·45	0·30	0·11	0·20	0·08

However, it should be remembered that the values of the burning velocity used by Lewis and von Elbe to calculate d_p and d_f were not very reliable for they were obtained by using the Gouy total area burner method and the visible cone. This method is known to give low values.

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The Supposed Dihydroindole Reduction Products of α-Cyano-o-nitrocinnamamide.

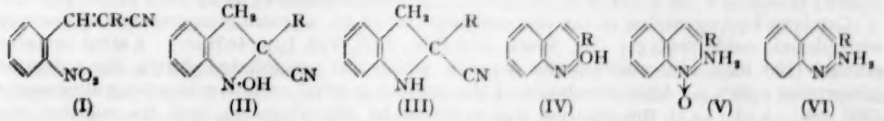
By (Miss) Jean M. Tyler.

[Reprint Order No. 5532.]

The reduction products of α-cyano-*o*-nitrocinnamamide (I*a*), previously supposed to be 2-carbamoyl-2-cyanodihydroindole (III*a*) and its *N*-hydroxy-derivative (II*a*), are shown to be 2-amino-3-carbamoylquinoline (VI*a*) and its *N*-oxide (V*a*) respectively. Treatment of the former with nitrous fumes does not cause the ring expansion (to a quinoline derivative), claimed by Heller and Wunderlich (*Ber.*, 1914, **47**, 1621), but merely replacement of the 2-amino-group by a hydroxyl group.

Heller and Wunderlich (*Ber.*, 1914, **47**, 1621) claimed ring expansion when the substance $C_{10}H_9ON_3$, believed to be 2-carbamoyl-2-cyanodihydroindole (III*a*), was treated with nitrous fumes at 60°, yielding nitrogen, and a new compound $C_{10}H_8O_2N_2$ in quantitative yield. Because this compound was readily converted by dilute alkali into the known 2-hydroxyquinoline-3-carboxylic acid (IV*b*) (Friedländer, *Ber.*, 1883, **16**, 1833; Mills and Watson, *J.*, 1910, **97**, 741) with liberation of ammonia, the structure 3-carbamoyl-2-hydroxyquinoline (IV*a*) was assigned to it.

The supposed carbamoyldihydroindole (III*a*) was prepared by reduction of α-cyano-*o*-nitrocinnamamide (I*a*), together with its "1-hydroxy-derivative" (II*a*), or by the reduction of the "hydroxy-derivative" (II*a*). These structures were based essentially on two suggested mechanisms for the production of the latter compound and on presumption of a *N*-hydroxy-group from a ferric chloride reaction; alkaline hydrolysis of the amides gave acids, which were identical with the reduction products, thought to be (II*b*) and (III*b*) (though no structural evidence was advanced) of α-cyano-*o*-nitrocinnamic acid



(I) (II) (III) (IV) (V) (VI)

(*a*) R = CO·NH$_2$ (*b*) R = CO$_2$H

(I*b*). Reduction of α-substituted *o*-nitrocinnamonitriles, however, produces 3-substituted 2-aminoquinolines and the corresponding *N*-oxides (Pschorr and Wolfes, *Ber.*, 1899, **32**, 3399; Rupe and Heckendorn, *Helv. Chim. Acta*, 1926, **9**, 981; Bauer, *Ber.*, 1938, **71**, 2226). This may be expected from a consideration of the configuration of an intermediate hydroxylamine derivative, particularly since the interaction of nitriles with hydroxylamine is well known (Migrdichian, "Chemistry of Organic Cyanogen Compounds," Reinhold Publ. Corpn., New York, 1947, p. 70 for collected references). Thus the "dihydroindole" compounds $C_{10}H_9ON_3$ and $C_{10}H_9O_2N_2$ are more probably 2-amino-3-carbamoylquinoline (VI*a*) and its *N*-oxide (V*a*). It has now been found that the compound $C_{10}H_9ON_3$ and dilute alkali yield one equivalent of ammonia under mild conditions which indicate the reaction of an amide rather than of a 2-aminoquinoline. The product of hydrolysis of $C_{10}H_9ON_3$ gave methyl and ethyl esters whose melting points and analyses agree with those for the 2-aminoquinoline-3-carboxylic esters (cf. VI*b*). The structure of (*a*) this acid and its methyl ester (Koller and Strang, *Monatsh.*, 1928, **50**, 144), and (*b*) the ethyl ester (Rupe and Heckendorn, *loc. cit.*) have been proved independently.

The methyl ester provided the original amide, $C_{10}H_9ON_3$, on ammonolysis and this therefore has the quinoline structure (VI*a*). The cycle (VI*a*) ⟶ (VI*b*) ⟶ ester ⟶ (VI*a*) is thereby effected and shows that reduction of α-cyano-*o*-nitrocinnamamide (I*a*) gives the quinoline derivatives (V*a*) and (VI*a*). Consequently the action of nitrous fumes does not involve ring expansion.

The reduction of α-cyano-*o*-nitrocinnamic acid (I*b*) at low temperature (cf. Heller and Wunderlich, *loc. cit.*) was repeated: the product and its methyl and ethyl ester gave analyses correct for the 3-substituted 2-aminoquinoline *N*-oxides. The melting point of the ethyl ester agreed with that recorded by Bauer (*loc. cit.*) who established the structure.

There seemed to be no reason why nitrous fumes at 60° should react specifically with the amino-group of 2-amino-3-carbamoylquinoline (VI*a*) yielding the phenol (IV*a*), rather than with the carbamoyl group. As the sole reference to the phenolic amide (IV*a*) is that of Heller and Wunderlich (*loc. cit.*), and as its m. p. was recorded as 291° and that of the isomeric amino-acid (VI*a*) is 290—292° (decomp.) (Rupe and Heckendorn, *loc. cit.*; Koller and Strang, *loc. cit.*), or >290° (Heller and Wunderlich, *loc. cit.*), an authentic specimen was prepared by ammonolysis of methyl 2-hydroxyquinoline-3-carboxylate. Re-investigation of the action of nitrous fumes on the amino-amide (VI*a*) showed that at 60° the principal product was the phenolic amide (IV*a*) (it was converted into methyl 2-hydroxyquinoline-3-carboxylate), but that at 100° some of the phenolic acid (IV*b*) was also produced. However, after reaction at 20—30° (Sudborough, *J.*, 1895, **67**, 602; cf. Bouveault, *Bull. Soc. chim.*, 1892, **9**, 368) the product, when esterified, yielded methyl 2-aminoquinoline-3-carboxylate and was therefore the amino-acid (VI*b*).

Experimental

Microanalyses were, in part, by the Micro-Analytical Laboratory of the Imperial College of Science and Technology, London.

2-Amino-3-carbamoylquinoline *N*-oxide (V*a*) was prepared by the reduction of α-cyano-*o*-nitrocinnamamide (I*a*) with zinc and dilute acetic acid (Heller and Wunderlich, *loc. cit.*). It was precipitated on dilution of the acid medium (accompanying 2-amino-3-carbamoylquinoline remained in solution), and formed yellow needles on crystallisation from ethanol (50%) to a constant m. p. [303° (decomp.); rapid heating; Heller and Wunderlich, *loc. cit.*, record m. p. >290°] (Found: C, 59·2; H, 4·6; N, 20·6. $C_{10}H_9ON_3$ requires C, 59·1; H, 4·5; N, 20·7%).

Catalytic hydrogenation of the cinnamamide (I*a*) (2 g.), at room temperature and pressure with platinic oxide (0·02 g.; *Org. Synth.*, 2nd Edn., Coll. Vol. I, p. 463) in 1 : 4 ethyl acetate–ethanol (100 ml.), also afforded the *N*-oxide, which was precipitated during the reduction (absorption: 99%). After dissolution of the product in ethyl acetate–ethanol–pyridine–water (300 ml.; 1 : 1 : 1 : 1) the catalyst was removed by centrifugation, and the solution was evaporated to dryness. The residue (1·75 g.) gave needles [1·10 g.; m. p. 303° (decomp.)] after two crystallisations from 1 : 1 aqueous ethanol (Found: C, 58·7; H, 4·4%).

2-Amino-3-carbamoylquinoline (VI*a*) was obtained most conveniently by reduction with zinc and aqueous ammonia at 80°, of the oxide (Heller and Wunderlich, *loc. cit.*). Crystallisation from water or 1 : 1 aqueous ethanol provided pale yellow needles, m. p. 237° (Heller and Wunderlich, *loc. cit.*, record 237—238°), which are not deliquescent though so described (Found: C, 63·9; H, 4·9; N, 22·5. $C_{10}H_9ON_3$ requires C, 64·3; H, 4·9; N, 22·5%).

Alkaline Hydrolysis of 2-Amino-3-carbamoylquinoline.—The amide (500 mg.) was heated for 45—55 min. with 0·25N-sodium hydroxide (40 ml.). The liberated ammonia was absorbed in saturated boric acid solution (40 ml.) and determined by titration with hydrochloric acid (approx. 0·04N) (Belcher and Godbert, "Semi-Micro Quantitative Organic Analysis," Longmans, Green and Co., London, 1947, p. 89) (Found: N, 7·2—7·5. Calc. for $C_{10}H_9ON_3$: 1N, 7·5%). The acid (480—490 mg.) separated on acidification of the solution with acetic acid. Decomposition occurred at the m. p. which was always sharp but variable, occasionally about 290°, but generally 326—328°; Heller and Wunderlich (*loc. cit.*) record >290°; Rupe and Heckendorn and Koller and Strang (*locc. cit.*) record 290—292° (decomp.). The high m. p. (326—328°) remained constant on crystallisation of the acid from water or 1% acetic acid (Found: C, 64·1; H, 4·6; N, 14·8. Calc. for $C_{10}H_8O_2N_2$: C, 63·8; H, 4·3; N, 14·9%).

The methyl ester, prepared (60—70%) by methanol–hydrogen chloride, formed yellow blades, m. p. 140—141° (Koller and Strang record 140—141°), from methanol (Found: C, 65·3; H, 5·2; N, 14·2. Calc. for $C_{11}H_{10}O_2N_2$: C, 65·3; H, 5·0; N, 13·9%). Methanol and sulphuric acid gave a 52% yield.

Ethyl 2-Aminoquinoline-3-carboxylate (XVII).—The ethyl ester, prepared (70—80%) by the hydrogen chloride method, formed yellow blades, m. p. 135° (Rupe and Heckendorn, *loc.*

cit., record 135°), from ethanol (Found: C, 67·1; H, 5·7; N, 12·9. Calc. for $C_{12}H_{12}O_2N_2$: C, 66·6; H, 5·6; N, 13·0%).

Ammonolysis of Methyl 2-Aminoquinoline-3-carboxylate.—To the ester (200 mg.) dissolved in ethanol, an equal volume of aqueous ammonia (*d* 0·880) was added, and the solution kept in a sealed tube for 18 days. The solvents were removed. Impurities were extracted from the residue (174 mg.; cloudy melt at 235—237°) by suspending it in benzene (2 ml.) and then in 0·5% sodium hydroxide (1 ml.). The amide crystallised from 1 : 1 aqueous ethanol as yellow needles (79 mg.), m. p. and mixed m. p. 236—237°.

Reduction of α-Cyano-o-nitrocinnamic Acid (I*b*).—Addition of water (2·5 ml.) to a hot solution of the acid [2·5 g.; prepared by Fiquet's method (*Ann. Chim. Phys.*, 1893, **29**, 490); (Found: C, 55·0; H, 3·1; N, 12·9. Calc. for $C_{10}H_6O_4N_2$: C, 55·0; H, 2·8; N, 12·8%)] in acetic acid (12·5 g.) afforded a fine precipitate of the acid, which was reduced by the addition of zinc dust (2·5 g.) at 30—40°. The mixture was stirred for a further 0·5 hr. (cf. Heller and Wunderlich, *loc. cit.*). Water (5 ml.) was added and the suspension filtered, washed and treated with 5% sodium hydroxide solution (30 ml.). Unchanged zinc was removed. *2-Aminoquinoline-3-carboxylic acid N-oxide* was precipitated by excess of 50% acetic acid (4 ml.), and after collection was washed and dried [1·99 g.; m. p. 305—307° (decomp.), rapid heating]. Crystallisation from 10% sodium acetate solution gave a yellow product, m. p. 318—320° (decomp.; rapid heating) (Heller and Wunderlich, *loc. cit.*, give m. p. >295°) (Found: C, 58·1; H, 4·1; N, 13·8. $C_{10}H_8O_3N_2$ requires C, 58·8; H, 4·0; N, 13·7%).

The foregoing acid was not esterified by methanol–hydrogen chloride but when refluxed for 18 hr. with sulphuric acid (2 ml.) in anhydrous methanol (25 ml.), gave the *methyl ester* (0·45 g. from 0·80 g.), yellow blades, m. p. 168·5—169° (from methanol) (Found: C, 60·5; H, 4·8; N, 12·8. $C_{11}H_{10}O_3N_2$ requires C, 60·5; H, 4·6; N, 12·8%).

The ethyl ester was prepared similarly but was extracted with ether. It had m. p. 137—138° (from ethanol) (Bauer, *loc. cit.*, records 141—142°) (Found: C, 62·4; H, 5·5; N, 12·2. Calc. for $C_{12}H_{12}O_3N_2$: C, 62·1; H, 5·2; N, 12·1%).

Methyl 2-Hydroxyquinoline-3-carboxylate.—This was prepared by refluxing 2-hydroxyquinoline-3-carboxylic acid [100 mg.; prepared by the reduction of α-carboxy-*o*-nitrocinnamic acid (Meyer, *loc. cit.*) (Found: C, 63·1; H, 3·8; N, 7·1. Calc. for $C_{10}H_7O_3N$: C, 63·5; H, 3·7; N, 7·4%)] with anhydrous methanol (5 ml.) and sulphuric acid (0·5 ml.) for 7 hr. (yield 75 mg.). It formed white blades, m. p. 186—186·5°, from methanol (Meyer, *loc. cit.*, gives 186°) (Found: C, 65·1; H, 4·9; N, 6·7. Calc. for $C_{11}H_9O_3N$: C, 65·0; H, 4·5; N, 6·9%).

3-Carbamoyl-2-hydroxyquinoline (IV*a*).—A solution of the methyl ester (120 mg.) in anhydrous methanol (10 ml.) and aqueous ammonia (*d* 0·880; 5 ml.) was kept in a sealed tube. The product began to separate during the first day. After 2 days, the solvents were removed, and the residue (m. p. 290°) gave cream-coloured needles (91 mg.), m. p. 290°, on crystallisation from water (25 ml.) (Heller and Wunderlich, *loc. cit.*, record 290—291°) (Found: N, 14·8. Calc. for $C_{10}H_8O_2N_2$: N, 14·9%).

Action of Nitrous Fumes on 2-Amino-3-carbamoylquinoline.—(a) *At* 60°. Two samples (each 300 mg.) of the amino-amide, suspended in water (30 ml.) and heated at 60°, were treated with a stream of nitrous fumes (cf. Heller and Wunderlich, *loc. cit.*) for 2 and 10 min. respectively. The products were collected after 3 hr. [254, 215 mg.; m. p. 236° (decomp.)] and were suspended in 5% sodium hydroxide solution (2 ml.). Unchanged amino-amide (106, 35 mg.) was filtered off. Acidification of the filtrate with 10% acetic acid gave precipitates (95, 148 mg.; m. p. 286—287°, 284—285°), which, after crystallisation from water, both melted at 290° (79, 127 mg.), and were identical (mixed m. p.) with authentic 3-carbamoyl-2-hydroxyquinoline. More unchanged amino-amide (65 mg. after crystallisation) was recovered when the original acid solution of the second experiment was acidified. The yields of the hydroxy-amide are 49 and 74% respectively.

A sample (150 mg.) of the hydroxy-amide was esterified by methanol–sulphuric acid, and after crystallisation from methanol the crude product (117 mg.) gave methyl 2-hydroxyquinoline-3-carboxylate, m. p. 185—186°.

(b) *At* 100°. The experiment with nitrous fumes (10 min.) was also conducted on a boiling-water bath. The product (277 mg.; m. p. 265—267°) did not contain unchanged amino-amide. It was extracted with 2% potassium carbonate solution (10 ml.); the residue gave cream-coloured needles of 3-carbamoyl-2-hydroxyquinoline (128 mg.), m. p. 289—290°, from water. Addition of 10% acetic acid to the alkaline filtrate gave 2-hydroxyquinoline-3-carboxylic acid, m. p. and mixed m. p. 330—331° (89 mg.) (from water).

Action of Nitrous Acid on 2-Amino-3-carbamoylquinoline.—0·5N-Sodium nitrite (3·2 ml.)

was gradually introduced below the surface of a solution of the amide (300 mg.) in 90% (w/v) sulphuric acid (3 ml.) at <30°. Nitrogen was evolved, and a cream-coloured precipitate separated. After dilution to 10 ml., the suspension was left for 1 hr. Unchanged amino-amide (42 mg.) was removed from the precipitate (367 mg.) by treatment with 5% sodium hydroxide solution (2 ml.), and the acidic material was reprecipitated (207 mg.; variable m. p. 306—308°, 290—292°) by 50% acetic acid (Found: N, 15·3. Calc. for $C_{16}H_8O_2N_2$: N, 14·9%). The methyl ester (m. p. 139° after two crystallisations from methanol) of the product (200 mg.) on admixture with methyl 2-amino-3-carbamoylquinoline (m. p. 139—140°) melted at 139°.

The author thanks Professor Gwyn Williams for his interest, the University of London for the award of a Postgraduate Studentship, the Department of Scientific and Industrial Research for a Maintenance Allowance, and Imperial Chemical Industries Limited for financial help.

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The Formation of Carbonium Ions by the Action of Metal Salts. Part I. The Reaction of Mercuric Chloride with Triphenylmethyl Chloride in Nitromethane.

By J. W. BAYLES, ALWYN G. EVANS, and J. R. JONES.

[Reprint Order No. 5590.]

In the reaction between mercuric chloride and triphenylmethyl chloride in nitromethane, equilibria exist involving triphenylmethyl ions. The concentration of these ions has been measured spectrophotometrically and the results show that the ionization of triphenylmethyl chloride involves the equilibria:

$$Ph_3CCl + HgCl_2 \rightleftharpoons Ph_3C^+HgCl_3^-$$

and

$$Ph_3C^+HgCl_3^- \rightleftharpoons Ph_3C^+ + HgCl_3^-$$

We have determined the changes in free energy and heat content for the forward reactions.

IN a preliminary communication (Bentley and Evans, *Research*, 1952, **5**, 535), it was shown that in nitromethane the ionization of triphenylmethyl chloride is very markedly enhanced by the presence of mercuric chloride, and the changes in free energy and heat content for the reaction between these two compounds were estimated spectrophotometrically. The measurements on this reaction have now been extended, and in this paper we give a detailed account of the results.

EXPERIMENTAL

Materials.—Nitromethane and triphenylmethyl chloride were obtained and purified as described by Evans, Jones, and Osborne (*Trans. Faraday Soc.*, 1954, **50**, 16). Mercuric chloride (B.D.H.) was purified by sublimation *in vacuo*, and stored in sealed capsules.

Spectra.—A solution of triphenylmethyl chloride in nitromethane was made up which was so dilute that the absorption of light by triphenylmethyl ions was not measurable. A solution of mercuric chloride in nitromethane was also prepared; this showed no light absorption in the spectral region used for estimating the triphenylmethyl ions. These colourless solutions became intensely yellow on mixing, and their light absorption was measured on a Unicam S.P. 500 Spectrophotometer. The spectrum is given in Fig. 1, curve *A*, together with that for triphenylmethyl alcohol in 98% sulphuric acid (curve *B*). In order that the shape of the two spectra may be easily compared, curve *B* has been calculated from results at other concentrations so that the optical density at the 430 mμ peak is the same as that of curve *A*. These calculations were carried out by using the direct proportionality between optical density and carbonium-ion concentration which has been established at all wave-lengths involved in the absorption for the sulphuric acid solution of triphenylmethyl alcohol (*idem, ibid.*, p. 470). It is seen that these two spectra are very similar, and since triphenylmethyl alcohol is completely

ionized in 98% sulphuric acid (Hantzsch, *Z. physikal. Chem.*, 1908, **61**, 257; Hammett and Deyrup, *J. Amer. Chem. Soc.*, 1933, **55**, 1900) according to the equation: $Ph_3C{\cdot}OH + 2H_2SO_4 \longrightarrow Ph_3C^+ + H_3O^+ + 2HSO_4^-$, this close similarity demonstrates the presence of triphenylmethyl ions in the nitromethane solutions of triphenylmethyl chloride and mercuric chloride.

Effect of Concentration.—Solutions containing different concentrations of reactants were made up by mixing, in various ratios, the nitromethane solutions of mercuric chloride and triphenylmethyl chloride described above. The concentration of triphenylmethyl ions in a mixed solution was calculated by assuming that $\int D_\lambda d\lambda$ is the same in this solution as in

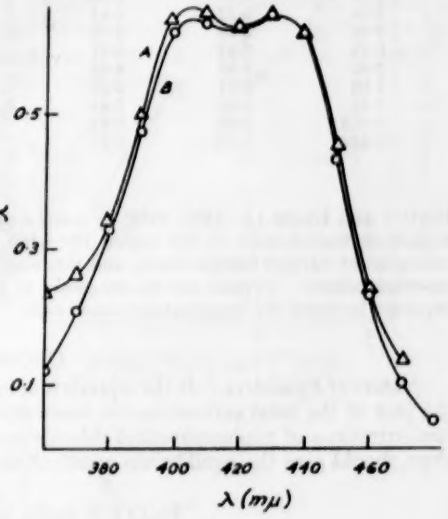

FIG. 1.

A, Mercuric chloride (total concn. $2{\cdot}542 \times 10^{-4}$ mole $l.^{-1}$) and triphenylmethyl chloride (total concn. $2{\cdot}754 \times 10^{-4}$ mole $l.^{-1}$) in nitromethane at 18°.

B. Triphenylmethyl alcohol (concn. $1{\cdot}711 \times 10^{-4}$ mole $l.^{-1}$) in 98% sulphuric acid.

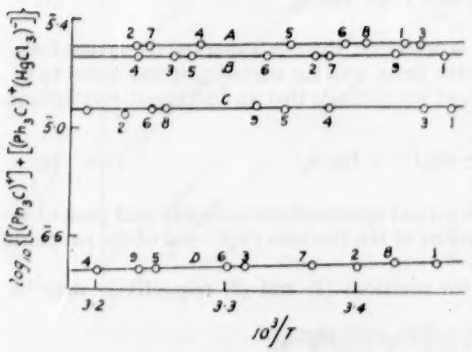

FIG. 2. *Total concentrations* $\times 10^4$ (*moles* $l.^{-1}$).

	A	*B*	*C*	*D*
Ph_3CCl ...	3·14	3·32	2·21	0·628
$HgCl_2$	3·62	3·41	2·28	0·725

98% sulphuric acid for the same carbonium-ion concentration. An alternative method of calculating the carbonium-ion concentration is to assume that $(D_\lambda)_{max.}$ is the same in the nitromethane solution as in 98% sulphuric acid for the same carbonium-ion concentration. Since the spectra shown in Fig. 1 are so similar this alternative method leads to values which are the same, within experimental error, as those obtained by the above method.

The carbonium-ion concentration was subtracted from the total mercuric chloride and total triphenylmethyl chloride concentrations to give the concentrations of these two reactants at equilibrium; this carbonium-ion concentration never amounted to more than 10% of the total triphenylmethyl chloride present. In Table 1 we give the results so obtained for two typical experiments.

Effect of Temperature.—Five solutions were made up in which the total amounts of mercuric

chloride and triphenylmethyl chloride were known, and the product of the equilibrium concentrations $[HgCl_2][Ph_3CCl]$, varied between $0{\cdot}4 \times 10^{-8}$ and $1{\cdot}0 \times 10^{-7}$ mole^2 l.$^{-2}$. The change of optical density of these solutions with change in temperature was measured as described by

TABLE 1. *Equilibrium concentrations of reactants in nitromethane.*

$10^5\{[Ph_3C^+] + [Ph_3C^+HgCl_3^-]\}$ (g.-ions l.$^{-1}$)	$10^4[HgCl_2]$ (mole l.$^{-1}$)	$10^4[Ph_3CCl]$ (mole l.$^{-1}$)	$10^5\{[Ph_3C^+] + [Ph_3C^+HgCl_3^-]\}$ (g.-ions l.$^{-1}$)	$10^4[HgCl_2]$ (mole l.$^{-1}$)	$10^4[Ph_3CCl]$ (mole l.$^{-1}$)
Experiment 1.			*Experiment* 2.		
3·84	5·04	4·74	3·95	5·36	5·85
2·70	5·15	2·80	3·71	5·39	4·63
2·04	5·22	1·84	3·18	5·44	3·43
3·56	3·98	4·76	2·53	5·51	2·25
3·13	2·94	4·81	1·35	5·62	1·11
2·39	1·93	4·88	0·81	5·68	0·55
1·66	2·54	2·39	4·02	4·21	5·85
1·18	2·59	1·41	3·40	3·12	5·91
0·815	2·63	0·94	2·63	2·04	5·99
0·464	1·03	0·97	1·91	2·69	2·93
			1·31	2·75	1·74
			0·563	1·09	1·19

Bentley and Evans (*J.*, 1952, 3468) by using a photomultiplier with an Ilford 601 filter having a maximum transmission in the region 400—460 mμ. The optical density of the solution was measured at various temperatures, and this was converted into carbonium-ion concentration as described above. Typical results are shown in Fig. 2, the points being numbered to show the sequence in which the temperature was varied.

DISCUSSION

Nature of Equilibria.—If the equilibrium involved in these experiments was of the form the plot of the total carbonium-ion concentration against the product of the equilibrium concentrations of triphenylmethyl chloride and mercuric chloride should be linear, and its slope should give the equilibrium constant for reaction (1). This plot is shown in Fig. 3,

$$Ph_3CCl + HgCl_2 \underset{(b)}{\overset{(a)}{\rightleftharpoons}} Ph_3C^+HgCl_3^- \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

curve *A*, for Experiment 2, Table 1, and it is seen that there is a marked departure from linearity. This experiment was carried out five times, and the curved plot was found to be quite reproducible. Because this plot is curved we conclude that an additional equilibrium exists which is of the form:

$$Ph_3C^+HgCl_3^- \underset{(b)}{\overset{(a)}{\rightleftharpoons}} Ph_3C^+ + HgCl_3^- \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

and that the ionic concentration which is measured spectrophotometrically and plotted in Fig. 3, curve *A*, is the sum of the concentrations of the free ions Ph_3C^+ and of the ion pairs $Ph_3C^+HgCl_3^-$.

The equilibrium constants K_1 and K_2 for reactions (1) and (2) respectively may be written:

$$K_1 = [Ph_3C^+HgCl_3^-]/\{[Ph_3CCl][HgCl_2]\}$$

and

$$K_2 = \frac{[Ph_3C^+][HgCl_3^-]}{[Ph_3C^+HgCl_3^-]} = \frac{[Ph_3C^+]^2}{[Ph_3C^+HgCl_3^-]}$$

from which

$$K_1 K_2 = [Ph_3C^+]^2/\{[Ph_3CCl][HgCl_2]\}$$

and

$$\frac{\{[Ph_3C^+] + [Ph_3C^+HgCl_3^-]\}}{[Ph_3CCl][HgCl_2]} = K_1 + \{K_1K_2/[Ph_3CCl][HgCl_2]\}^{\frac{1}{2}} \quad . \quad . \quad (3)$$

Thus, if instead of plotting the total carbonium-ion concentration

$$\{[Ph_3C^+] + [Ph_3C^+HgCl_3^-]\}$$

against $[Ph_3CCl][HgCl]$, as in Fig. 3, we plot $\{[Ph_3C^+] + [Ph_3C^+HgCl_3^-]\}/[Ph_3CCl][HgCl_2]$ against $\{[Ph_3CCl][HgCl_2]\}^{-\frac{1}{2}}$ we should obtain a straight line, according to equation (3), of slope $\sqrt{K_1K_2}$ and of intercept K_1. This plot is shown in Fig. 4 for the two experiments

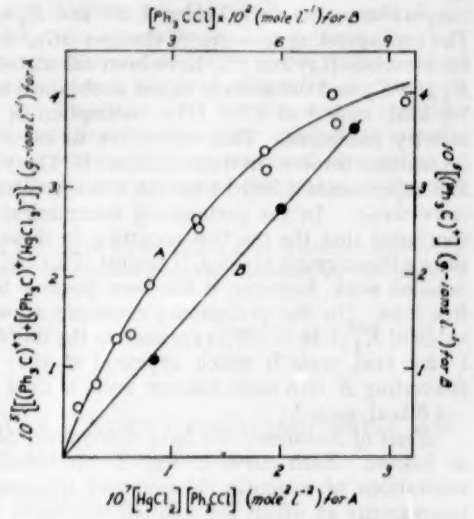

FIG. 3.

A, Nitromethane solution containing Ph_3CCl and $HgCl_2$.
Dependence of carbonium-ion concentration on $[Ph_3CCl][HgCl_2]$.

B, Nitromethane solution containing only Ph_3CCl.
Dependence of carbonium-ion concentration on $[Ph_3CCl]$.

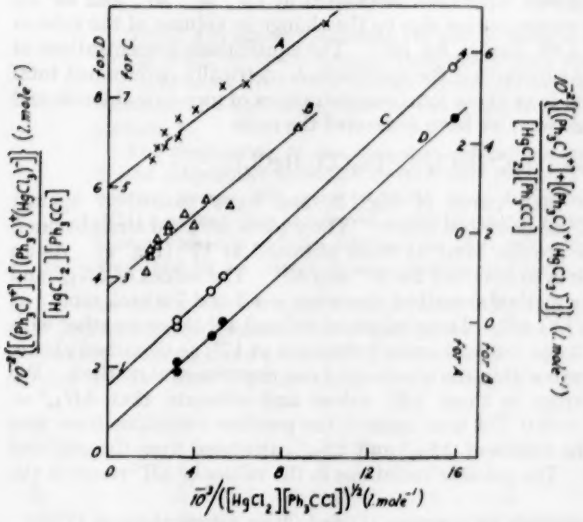

FIG. 4. *Plot of equation* (3).

The figures on the four vertical scales refer from left to right, respectively, to

1 ● 40°.
2 ○ 30°.
3 × 17° (Experiment 1, Table 1).
4 △ 17° (Experiment 2, Table 1).

given in Table 1. The fact that good straight lines are obtained demonstrates the existence of the two equilibria (1) and (2) in these solutions. {The assumption that the extinction coefficients of the ion pair $Ph_3C^+HgCl_3^-$ and of the free ion Ph_3C^+ in nitromethane are the same as for the free ion in concentrated sulphuric acid is strongly supported by the following facts: (*a*) the shapes of the spectra in these two solvents are very similar; (*b*) we find that the shape of the spectrum is constant over the whole range of the concentration product, $[Ph_3CCl][HgCl_2]$, used in the experiments.} The experiments were carried out five times, and values of K_1 and K_2 were determined as described above for each experiment. The

concentrations of reactants used in these plots are expressed in the units mole $l.^{-1}$ and g.-ion $l.^{-1}$, and the average values of K_1 and K_2 so obtained are 80·4 $mole^{-1}$ l. and $2{\cdot}39 \times 10^{-5}$ mole $l.^{-1}$ respectively. We have converted these average values to mole fraction units, using the known values for the density of nitromethane at different temperatures (Int. Crit. Tables, **3**, 28) and K_1 and K_2 are given in these units in Table 2. The corresponding free-energy changes ΔG_{1a}° ($= -\boldsymbol{R}T \ln K_1$) and ΔG_{2a}° ($= -\boldsymbol{R}T \ln K_2$) for reactions (1*a*) and (2*a*) have been calculated from the values in mole fraction units of K_1 and K_2, and the average values so obtained are $\Delta G_{1a}^{\circ} = -4{\cdot}2$ kcal. $mole^{-1}$ and $\Delta G_{2a}^{\circ} = 7{\cdot}8$ kcal. $mole^{-1}$ at 17°. (The assumption is made here, that the reactants have unit activity coefficient. This we believe to be valid because of the very small ionic concentrations involved in these solutions.) The values of ΔG_{1a}° and ΔG_{2a}° obtained in these five experiments differed from the average values by less than $\pm 0{\cdot}2$ and $\pm 0{\cdot}6$ kcal. $mole^{-1}$ respectively. In the preliminary communication (Bentley and Evans, *loc. cit.*) it was concluded that the reaction occurring in these solutions was that shown in equation (1) since a linear graph of $[Ph_3C^+]$ against $[Ph_3CCl][HgCl_2]$ was obtained. In the present more detailed work, however, it has been possible to detect the dissociation of ion pairs into free ions. [In the preliminary communication, ΔG_{1a}° was calculated from the average value of K_1 ($1{\cdot}46 \times 10^2$), expressed in the units l. $mole^{-1}$, and this gave the value of ΔG_{1a}° ($-2{\cdot}9$ kcal. $mole^{-1}$) which appeared in that communication. If the method of first converting K into mole fraction units is used the ΔG_{1a}° obtained from this K_1 value is $-4{\cdot}6$ kcal. $mole^{-1}$.]

Heats of Reaction.—We have determined ΔH_{1a}° and ΔH_{2a}° for reactions (1*a*) and (2*a*) as follows. Each curve in Fig. 2 corresponds to a solution for which the total concentrations of mercuric chloride and triphenylmethyl chloride are known at 17°, the temperature at which the solution was made up. The total concentrations of mercuric chloride and triphenylmethyl chloride have been calculated at 15°, 20°, 30°, and 40° by allowing for the small change in concentration due to the change in volume of the solvent with changing temperature (Int. Crit. Tables, *loc. cit.*). The equilibrium concentrations of these reactants were obtained by subtracting the spectrophotometrically determined total triphenylmethyl-ion concentration from these total concentrations of mercuric chloride and triphenylmethyl chloride. In this way, we have evaluated the ratio

$$\{[Ph_3C^+] + [Ph_3C^+HgCl_3^-]\}/[Ph_3CCl][HgCl_2]$$

at 15°, 20°, 30°, and 40° for each curve of Fig. 2, and have plotted it against $\{[Ph_3CCl][HgCl_2]\}^{-1}$ as in the analysis described above. These plots are good straight lines, which within experimental error are the same as those obtained at 17° (Fig. 4). As an example, we give in Fig. 4 the plots so obtained for 30° and 40°. The values of ΔG_{1a}° and ΔG_{2a}° obtained from Fig. 4 by the method described above are $-4{\cdot}2$ and 7·9 kcal. $mole^{-1}$ at 30°, and $-4{\cdot}4$ and 8·3 kcal. $mole^{-1}$ at 40°. These values at 30° and 40° taken together with the corresponding values of $-4{\cdot}2$ and 7·8 kcal. $mole^{-1}$ obtained at 17°, as described above, show that ΔH_{1a}° and ΔH_{2a}° are zero within the accuracy of our experimental method. We have considered the possible errors in these ΔH° values and estimate that $\Delta H_{1a}^{\circ} = 0{\cdot}0 \pm 2$ kcal. $mole^{-1}$ and $\Delta H_{2a}^{\circ} = 0{\cdot}0 \mp 4$ kcal. $mole^{-1}$, the possible variations from zero being in opposite directions. The values of ΔS_{1a}° and ΔS_{2a}° calculated from the ΔG° and ΔH° values are given in Table 2. The possible variations in the values of ΔH° result in the

TABLE 2. *Thermodynamic quantities for reactions* (1) *and* (2) *in nitromethane at* 17·0°.

Reaction	K_1 (mole fraction)	K_2 (mole fraction)	ΔG_{1a}° (kcal. $mole^{-1}$)	ΔG_{2a}° (kcal. $mole^{-1}$)	ΔH_{1a}° (kcal. $mole^{-1}$)	ΔH_{2a}° (kcal. $mole^{-1}$)	ΔS_{1a}° (cal. $deg.^{-1}$ $mole^{-1}$)	ΔS_{2a}° (cal. $deg.^{-1}$ $mole^{-1}$)
1	$1{\cdot}5 \times 10^2$	—	−4·2	—	0·0	—	15	—
2	—	$1{\cdot}3 \times 10^{-4}$	—	7·8	—	0·0	—	−27

limits of accuracy for the ΔS_{1a}° and ΔS_{2a}° values being 15 ± 7 and -27 ∓ 14 cal. $deg.^{-1}$ $mole^{-1}$ respectively.

Dissociation of Ion Pairs.—It is interesting that in the nitromethane solution of triphenylmethyl chloride and mercuric chloride the dissociation of the ion pairs

$Ph_3C^+HgCl_3$ can be detected, since for nitromethane solutions containing only RCl no dissociation of ion pairs has been detected over a wide variety of types of R (Bentley, Evans, and Halpern, *Trans. Faraday Soc.*, 1951, **47**, 711; Evans, Jones, and Osborne, *loc. cit.*).* We have repeated the earlier work on nitromethane solutions containing only triphenylmethyl chloride (Bentley, Evans, and Halpern, *loc. cit.*), to see if we could obtain any indication of ion-pair dissociation, but none was detectable (see Fig. 3, curve *B*). This observed difference in the occurrence of ion-pair dissociation for these two systems might be caused if the distance apart of the positive and negative centres in the ion pair $Ph_3C^+HgCl_3^-$ were greater than in the ion pair $Ph_3C^+Cl^-$. To test this, and to elucidate other points, we are extending these experiments to different organic halides and metallic compounds, since a knowledge of the factors governing the formation and dissociation of such ion-pair complexes is fundamental to the understanding of the action of Friedel–Crafts catalysts.

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CHEMISTRY DEPT., UNIVERSITY COLLEGE, CARDIFF. [*Received, July 26th*, 1954.]

Simple Pyrimidines. Part II.† 1 : 2-*Dihydro*-1-*methylpyrimidines and the Configuration of the* N-*Methyluracils.*

By D. J. BROWN, EARL HOERGER, and S. F. MASON.

[Reprint Order No. 5663.]

2- and 4-Hydroxypyrimidine are proved to exist in solution largely in the lactam form, by spectrographic comparison with their *N*-methyl derivatives (for differences from the *O*-methyl derivatives see Part I *). The tautomeric hydrogen of 4-hydroxypyrimidine was found to favour position 1 rather than position 1.

The preparation of the *N*-methyl derivatives involved *N*-methylation of 2- and 4-hydroxypyrimidine to (III) and (VII). The latter, as well as the missing isomer (V), were prepared from 4-hydroxy-2-mercaptopyrimidine (VIII), so that their structures might be related to those of the corresponding *N*-methyluracils, whose orientations (formerly doubtful) have now been confirmed by an unambiguous synthesis of 1-methyluracil (XI; R = H).

IT has been shown (Brown and Short, *J.*, 1953, 331) that the substances commonly known as 2- and 4-hydroxypyrimidine have spectra very different from those of 2- and 4-methoxypyrimidine and, on these grounds, they are considered to exist largely as the tautomeric amides (II, IV, and VI) (for earlier work pointing to this conclusion see Marshall and

(Ia) (Ib) (Ic) (II; R = H) (III; R = Me) (IV; R = H) (V; R = Me) (VI; R = H) (VII; R = Me)

Walker, *J.*, 1951, 1004; Boarland and McOmie, *J.*, 1952, 3716). To obtain more positive evidence synthesis of the three possible *N*-methyl derivatives (III, V, and VII) was undertaken. In addition, comparison of the isomers (V) and (VII) might make it possible to state to which nitrogen atom the hydrogen in "4-hydroxypyrimidine," which is non-

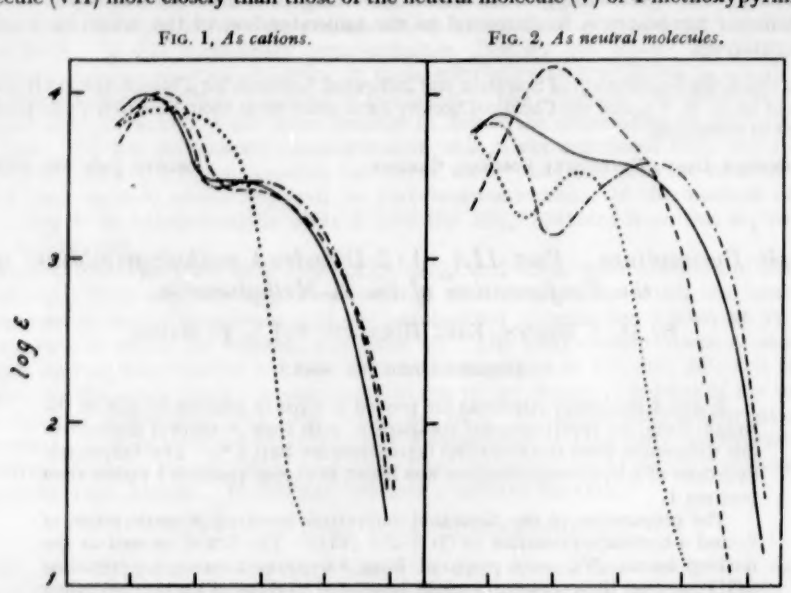
* Evans, Price, and Thomas (*Trans. Faraday Soc.*, in the press) have recently obtained evidence for the dissociation of ion pairs, R^+Cl^-, for *p*-methyl substituted triphenylmethyl chlorides in pure acetic acid.

† Part I, *J.*, 1953, 331.

symmetrical, is attached. The correct orientation of the methyl group in (V) and (VII) was found by the preparation of the former from the 2-methylthio-derivative (IX) and the hydrolysis of (IX) to 1-methyluracil (XI; R = H). The orientation of 1- and 3-methyluracil in the literature was not beyond doubt, and so has been re-investigated.

Spectroscopy.—The ultra-violet absorption spectra of 2-hydroxypyrimidine resemble those of its *N*-methyl derivative (III) more closely than those of 2-methoxypyrimidine (Table), indicating that it exists largely in the amide form (II). The spectrum of the cation of 4-hydroxypyrimidine is closely similar to those of the cations of the *N*-methyl derivatives (V) and (VII) and differs from that of the cation of 4-methoxypyrimidine (Fig. 1 and Table), whilst the spectrum of its neutral molecule resembles that of the neutral molecule (VII) more closely than those of the neutral molecule (V) or 4-methoxypyrimidine

FIG. 1, *As cations.* FIG. 2, *As neutral molecules.*



(Fig. 2 and Table). Thus it is highly probable that the tautomerism in the case of 4-hydroxypyrimidine favours the lactam forms, with (VI) predominating at the expense of (IV). The spectrum of the iodide, obtained by the prolonged action of methyl iodide on 4-hydroxypyrimidine, is similar to the spectra of the cations of (V) and (VII) (see Table), suggesting that this iodide possesses the structure (I; R = Me).

The long-wave-length band of the neutral molecule of the *N*-methyl derivative (V) is more intense and lies at a shorter wave-length than that of the neutral molecule of its isomer (VII), differences which are general between the spectra of the neutral molecules of similar heterocyclic carbonyl compounds (Berson, *J. Amer. Chem. Soc.*, 1953, **75**, 3521).

The spectra of the cations of the *N*-methyl derivatives (V) and (VII) closely resemble one another, however, owing to the formation of similar chromophore systems, each being a resonance hybrid of the principal forms (I*a*, *b*, and *c*) upon the addition of a proton. The shorter wave-length of maximum absorption in the spectrum of the neutral molecule of the form (V) may be ascribed to the greater energy required for the transition from the ground state, of which (V) is the main canonical structure, to the excited state, in which the

polar structure (XII) is predominant, than for the transition from the ground state of the isomer represented principally by the homopolar structure (VII), to the excited state, which partakes heavily of the polar structure (XIV), owing to the greater separation of charge in (XII) than in (XIV). However, the greater separation of charge in (XII) confers upon the excited state of 1-methyl-4-oxo-compound a dipole moment larger than that of the excited state of its isomer, so that the difference between the dipole moments of the ground and the excited states, the transition moment, and thus the intensity of the absorption of radiation, is greater in the former than in the latter. The ratio of the dipole moments of (XII) and (XIV), and hence the ratio of the transition moments of the isomers (V) and (VII) if the contributions of (XII) and (XIV) to the ground states of these substances are small, may be taken as approximately equal to the ratio of the squares of the distances between the charged centres in each of these structures, namely, 0·35 (Berson, *loc. cit.*), a value in good agreement with the ratio of the integrated intensities of the long-wave-length bands in the spectra of the isomeric compounds, namely, 0·33. The values of the integrated intensities of the long-wave-length bands in the spectra of 2- and 4-hydroxypyrimidine, the 1-methyl-2-oxo-compound (III), and the 3-methyl-4-oxo-compound (VII) are in good quantitative agreement, again indicating that 4-hydroxypyrimidine exists largely in the form of the lactam (VI).

In the infra-red region, the methyl derivatives (III), (V), and (VII), like 2- and 4-hydroxypyrimidine (Part I), possess a very strong absorption band in the 1600—1700-cm.$^{-1}$ region, due to the carbonyl bond stretching vibrations. In (III) and (VII) the band lies at 1670 and 1675 cm.$^{-1}$ respectively, *i.e.*, within the region 1700—1665 cm.$^{-1}$ typical of αβ-unsaturated ketones (Cromwell, Miller, Johnson, Frank, and Wallace, *J. Amer. Chem. Soc.*, 1949, **71**, 3337), whilst in (V) the band lies at 1653 cm.$^{-1}$, *i.e.*, within the region 1670—1650 cm.$^{-1}$ typical of αβ : α′β′-unsaturated ketones (Cromwell *et al.*, *loc. cit.*).

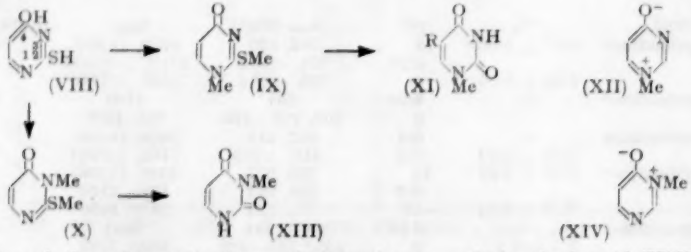
Compound	pK_a	pH	$\lambda_{max.}$ (mμ)	$\varepsilon_{max.}$	$10^7 I_a$ [f] (l. cm.$^{-2}$ mole^{-1})
2-Hydroxypyrimidine [a]	9·17 ± 0·06 [a]	13	292, 220	4550, 11,600	
		6·21	298, <215	4710, >10,000	2·10
	2·24 ± 0·04	0	309, <215	5650, >1710	
2-Methoxypyrimidine [b]	—	6·98	264	4780	1·67
		0	309, 273—274	708, 4900	
1-Methyl-2-pyrimidone	—	6·0	302, 215	5400, 10,000	2·17
	2·50 ± 0·04	0·3	313, <215	7102, >6360	
4-Hydroxypyrimidine [c]	8·60 ± 0·02 [c]	13	263, 227	3280, 11,090	
		6·2	260, 223	3740, 7320	2·3
	1·69 ± 0·04	−1 [f]	251, 224	2970, 4890	
4-Methoxypyrimidine [c]	—	6·95	247—248	3350	1·53
	2·5 ± 0·2	0	238,[h] 227—228	6800, 7740	
1 : 6-Dihydro-1-methyl-6-oxopyrimidine	—	5·0	269, 221	3900, 6810	2·20
	1·84 ± 0·03	−0·4 [g]	258, 226	2940, 9080	
1 : 4-Dihydro-1-methyl-4-oxopyrimidine	—	6·0	240	14,640	7·30
	ca. 1·8	−0·4 [g]	252,[h] 229	2640, 10,200	
1-Methyl-5-nitrouracil	7·20 ± 0·02 [a]	4·0	310, 240	11,400, 8240	—
3-Methyl-5-nitrouracil	—	4·0	298, 235	9440, 8160	—
1-Methyl-5-bromouracil	—	4·0	284, <215	9000, >9370	—
3-Methyl-5-bromouracil	—	4·0	275, <215	6960, >9720	—
1 : 4(3 : 4)-Dihydro-1 : 3-dimethyl-4-oxopyrimidinium iodide [d]	—	7	261, 230	2610, 8640	—

[a] L. N. Short, unpublished work. [b] Boarland and McOmie, *J.*, 1952, 3716. [c] Part I. [d] Corr. for iodide ion absorption. [e] Acidic pK_a. [f] In 5N-H_2SO_4. [g] In 2·5N-HCl. [h] Shoulder. [i] I, the integrated intensity, was calculated according to the approximate relation, $I = \varepsilon_{max.}\Delta\nu$, where $\Delta\nu$ is the band width in cm.$^{-1}$ at the point where $\varepsilon = \frac{1}{2}\varepsilon_{max.}$

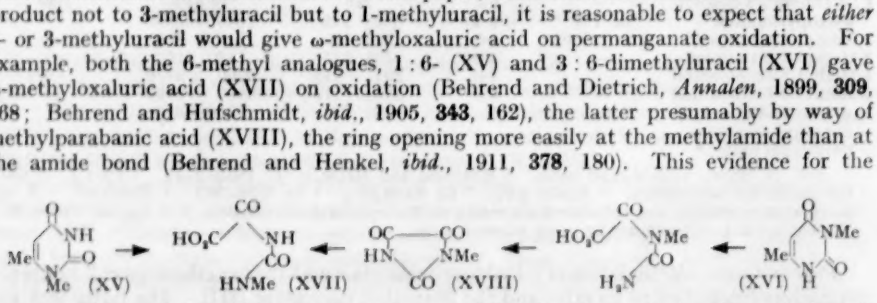
Preparations.—Methylation of 2-hydroxypyrimidine with diazomethane gave 2-methoxypyrimidine (identified as picrate) and the *N*-methyl derivative (III). The latter was also produced in small yield by heating 2-methoxypyrimidine at 190°. Similar methylation of 4-hydroxypyrimidine gave some 4-methoxypyrimidine (picrate) and a substance, m. p. 124°, which could be either (V) or (VII). The same *N*-methyl compound was formed on heating 4-methoxypyrimidine. It was identified as the isomer (VII) as follows: 2-Thiouracil (VIII) was methylated to a mixture of *N*-methyl derivatives (IX) and (X).

The latter on desulphurization with Raney nickel gave the above substance of m. p. 124°. The orientation of (X) follows from its hydrolysis to 3-methyluracil * (XIII; see below). The *N*-methyl compound (V) was not found among the methylation products of 4-hydroxypyrimidine but was obtained by the desulphurization of (IX), the orientation of which is known from its hydrolysis to 1-methyluracil (XI; R = H). When 4-hydroxypyrimidine reacted with methyl iodide, the *NN'*-dimethiodide (I; R = Me) was found in small yield. It was distinguished from the two theoretically possible *NN*-dimethyl isomers spectrographically (see p. 212).

1- *and* 3-*Methyluracil.* The position of the methyl group in the *N*-methyluracils has been accepted for nearly 50 years on the basis of Johnson and Heyl's work (*Amer. Chem. J.*, 1907, **37**, 634). Among the more important structures directly depending on these configurations are the pyrimidine nucleosides (Levene and Tipson, *J. Biol. Chem.*, 1934, **104**, 385; Bredereck, Haas, and Martini, *Chem. Ber.*, 1948, **81**, 307), the antibiotics amicetin (Flynn, Hinman, Caron, and Woolf, *J. Amer. Chem. Soc.*, 1953, **75**, 5867), and grisein (Kuehl, Bishop, Chaiet, and Folkers, *ibid.*, 1951, **73**, 1770), besides many synthetic pyrimidines. The proof of structure for 1- and 3-methyluracil advanced by Johnson and Heyl (*loc. cit.*) is not convincing. It depends on the melting point of the nitration product of the higher-melting *N*-methyluracil being nearer to that of 3-methyl-5-nitrouracil [263—265° (decomp.)] than to that of 1-methyl-5-nitrouracil [255—257° (decomp.), or even 264°; see Experimental section]. A further point was made that the methylation product had no water of crystallization whereas 1-methyl-5-nitrouracil had been reported as the monohydrate at room temperature. However, no direct comparison or mixed m. p.s appear to have been made with authentic specimens of *N*-methyl-5-nitrouracils made by an unquestionable route (Behrend and Thurm, *Annalen*, 1902, **323**, 160; Behrend and Hesse, *ibid.*, 1903, **329**, 348).



Kuehl *et al.* (*loc. cit.*) oxidized 3-methyluracil to ω-methyloxaluric acid (XVII). Apart from the confusion in formulæ 1 and 2 of that paper, which show the relation of the oxidation product not to 3-methyluracil but to 1-methyluracil, it is reasonable to expect that *either* 1- or 3-methyluracil would give ω-methyloxaluric acid on permanganate oxidation. For example, both the 6-methyl analogues, 1 : 6- (XV) and 3 : 6-dimethyluracil (XVI) gave ω-methyloxaluric acid (XVII) on oxidation (Behrend and Dietrich, *Annalen*, 1899, **309**, 268; Behrend and Hufschmidt, *ibid.*, 1905, **343**, 162), the latter presumably by way of methylparabanic acid (XVIII), the ring opening more easily at the methylamide than at the amide bond (Behrend and Henkel, *ibid.*, 1911, **378**, 180). This evidence for the



structure of 3-methyluracil is thus inconclusive. Whitehead's synthesis of 3-methyluracil (*J. Amer. Chem. Soc.*, 1952, **74**, 4267) is also ambiguous.

However, the following synthesis is unambiguous. Methyl β-methylaminopropionate

* Uracil is here considered as 2 : 4-dihydroxypyrimidine, and cytosine as 4-amino-2-hydroxypyrimidine.

was heated with cyanic acid to give on ring closure 5 : 6-dihydro-1-methyluracil. The 5-bromo-derivative of this was dehydrobrominated on melting, to 1-methyluracil (XI; R = H), which was converted into 5-bromo-1-methyl- (XI; R = Br) and 1-methyl-5-nitrouracil (XI; R = NO_2). Comparison by mixed m. p., paper-chromatography, and ultra-violet spectra (see Table) with the two *N*-methyluracils and the nitro- and bromo-derivatives prepared from them showed that the structure assigned by Johnson and Heyl was correct. The isomer, m. p. *ca.* 175°, is 3-methyluracil (XIII); that of m. p. *ca.* 233° is 1-methyluracil (XI; R = H).

Another related doubtful structure was investigated. Johns (*J. Biol. Chem.*, 1912, **11**, 73) methylated 5-nitrocytosine. The *N*-methyl derivative on acid hydrolysis was said, without direct comparison, to give 1-methyl-5-nitrouracil (XI; R = NO_2). Repetition and direct comparison with both 1- and 3-methyl-5-nitrouracil showed Johns's formulation of his product as 1-methyl-5-nitrocytosine to be correct. It follows that Johns's 4 : 5-diamino-1-methyl-2-pyrimidone (Johns, *ibid.*, 1914, **17**, 1) is also correctly designated. There is no longer any doubt of the orientation of the *N*-methylation products of cytosine (Johnson and Clapp, *ibid.*, 1909, **5**, 49; Hilbert, *J. Amer. Chem. Soc.*, 1934, **56**, 190) or of 2-hydroxy-4-methylamino-5-nitropyrimidine (Johns, *J. Biol. Chem.*, 1913, **14**, 3; 1914, **17**, 1) as direct comparisons were made with substances whose orientation has been confirmed above.

Experimental

Analyses were by Mr. P. R. W. Baker, Beckenham.

Spectra.—Ultra-violet absorption spectra were measured with a Hilger Uvispek H700/301 Quartz Spectrophotometer, with buffer solutions having the pH values recorded in the Table. The solvents were 0·01M-acetate buffer (for pH 3·8—5·7), and 0·01M-phosphate buffer (for pH 6·0—7·9), together with 0·1N-potassium hydroxide (pH 13) and N-hydrochloric acid (pH 0).

Infra-red absorption spectra were measured with a Perkin–Elmer Model 12C recording spectrometer, with a sodium chloride prism, the compounds being compressed into a disc with potassium bromide.

1 : 2-*Dihydro*-1-*methyl*-2-*oxopyrimidine*.*—2-Hydroxypyrimidine (1·0 g.; Brown, *Nature*, 1950, **165**, 1010) was suspended in ethereal diazomethane (from 5 g. of *N*-nitrosomethylurea, 70 ml. of ether, and 20 ml. of 40% potassium hydroxide solution). Evolution of nitrogen was slow and the crystals were crushed occasionally; a new solid gradually appeared. After 2 days at room temperature the product (52%; m. p. 122—123°) was collected. Repeated recrystallization from acetone (10 parts; charcoal) gave colourless 1 : 2-*dihydro*-1-*methyl*-2-*oxopyrimidine*, m. p. 127—128° (Found: C, 54·65; H, 5·4; N, 25·45. $C_5H_6ON_2$ requires C, 54·55; H, 5·5; N, 25·45%). The *picrate* recrystallized from ethanol (80 parts) as yellow needles, m. p. 162—164° (Found: C, 39·0; H, 2·75. $C_{11}H_9O_8N_5$ requires C, 38·95; H, 2·65%).

The ethereal filtrate from the reaction mixture was distilled, to give 2-methoxypyrimidine (17%, b. p. 70—80°/20 mm.). It was redistilled and its picrate made. Authentic 2-*methoxypyrimidine picrate*, from ethanol (15 parts), had m. p. 105—106° (Found: N, 20·7. $C_{11}H_9O_8N_5$ requires N, 20·65%).

2-Methoxypyrimidine (1 g.) was heated at 190—200° for 3 hr. Unchanged 2-methoxypyrimidine (0·7 g.) was distilled off (bath 120°; 10 mm.). The crystalline residue was identified as 1 : 2-dihydro-1-methyl-2-oxopyrimidine by its picrate.

1 : 6-*Dihydro*-1-*methyl*-6-*oxopyrimidine*.—(a) *By methylation.* 4-Hydroxypyrimidine (1·0 g.) was methylated as was the 2-isomer. After 2 days the solid was removed and concentration almost to dryness gave a second crop (total yield, 51%). Several recrystallizations from chloroform (5 parts) gave thick colourless prisms of the 6-*oxo*-derivative, m. p. 125—126° (Found: C, 54·8; H, 5·4; N, 25·4%). The *picrate*, from ethanol (100 parts), had m. p. 175—176° (Found: N, 20·8. $C_{11}H_9O_8N_5$ requires N, 20·65%).

From the combined mother-liquors (above) there was obtained 4-methoxypyrimidine (9%; b. p. 70—80°/20 mm.; Brown and Short, *loc. cit.*), identified as picrate. Authentic 4-*methoxypyrimidine picrate*, from ethanol (30 parts), had m. p. 123—124° (Found: C, 39·0; H, 3·2; N, 20·0. $C_{11}H_9O_8N_5$ requires C, 38·95; H, 2·65; N, 20·65%).

(b) *From* 4-*methoxypyrimidine*. 4-Methoxypyrimidine (13 mg.) was heated at 190—195°

* This compound might elsewhere be named 1-methyl-2-pyrimidone. Similar alternative names might be used elsewhere for analogous compounds.

(sealed tube) for 2 hr. Sublimation (bath 100°; 20 mm.) then gave the *N*-methyl compound (6 mg.; m. p. 121—124°), identified by mixed m. p. with the previous product.

(c) *By desulphurization.* 1 : 6-Dihydro-1-methyl-2-methylthio-6-oxopyrimidine (see below; 1·5 g.) was boiled in water (25 ml.) with Raney nickel (8 g., wet) for 2 hr. The filtered solution was saturated with sodium chloride and extracted with chloroform (continuously for 24 hr.). The residue from the evaporated extract recrystallized from *cyclo*hexane (120 ml.), giving the above-mentioned product (34%), m. p. 123—124°.

1 : 4(3 : 4)-*Dihydro*-1 : 3-*dimethyl*-4-*oxopyrimidinium iodide*.—A solution of 4-hydroxypyrimidine (200 mg.), methyl iodide (0·4 ml.; 2·7 mols.), and methanol (4 ml.) was stored for 30 days at room temperature. Removal of solvent (reduced pressure) left a red oil which solidified. Recrystallization from ethanol (100 parts) gave 17% of tan-coloured *iodide*, m. p. 205—206° (Found: N, 11·1; I, 50·6. $C_6H_9ON_2I$ requires N, 11·1; I, 50·35%).

Dihydro-N-*methyl*-2-*methylthio*-*oxopyrimidines*.—To 2-thiouracil (50 g.) in 5N-sodium hydroxide (220 ml.) methyl sulphate (5 × 20 ml.) was added at <50°. The mixture was finally warmed to 70°, then chilled overnight. 1 : 6-*Dihydro*-1-*methyl*-2-*methylthio*-6-*oxopyrimidine* (19·4 g.; m. p. 122—123°) was filtered off, the filtrate repeatedly extracted at room temperature with chloroform, and the chloroform distilled off, leaving crystalline residues. The first 3 extracts (25 ml. each) gave impure material from which, by recrystallization from ethanol, more of the previous lactam (3·2 g.; m. p. 120—122°) was obtained (total yield, 37%). Recrystallization from water (10 parts) gave colourless plates, m. p. 122—123° (Found: C, 46·2; H, 4·95; N, 18·0. $C_6H_8ON_2S$ requires C, 46·15; H, 5·15; N, 17·95%).

The next few extracts (100 ml. each) yielded progressively higher melting material until at the nineth extraction nearly pure 1 : 4-*dihydro*-1-*methyl*-2-*methylthio*-4-*oxopyrimidine* was obtained (1·7 g.; m. p. 166—167°). Seventeen further extractions (100 ml. each) gave diminishing amounts of comparable material. Thereafter, further extractions gave less pure material (*e.g.*, 49th extract: 0·03 g., m. p. 110—132°). The purer residues were combined and recrystallized from ethanol (4 parts). Lower-melting fractions were repeatedly recrystallized and mother-liquors reworked, the total yield being 38%. Final recrystallization gave colourless plates, m. p. 168—169° (Found: C, 46·3; H, 5·2; N, 17·9%).

1-*Methyluracil*.—The last-mentioned compound (1·0 g.) was refluxed for 2½ hr. with hydrochloric acid (*d* 1·1; 8 ml.) and brought to pH 3 with 10N-sodium hydroxide (yield, 72%). Recrystallization from water (22 parts) gave colourless needles of 1-methyluracil, m. p. 232—233° (Found: C, 47·5; H, 4·4; N, 22·6. Calc. for $C_5H_6O_2N_2$: C, 47·6; H, 4·8; N, 22·2%). It was identical (mixed m. p.; paper chromatography) with authentic material prepared as below.

1 : 4-*Dihydro*-1-*methyl*-4-*oxopyrimidine*.—1 : 4-Dihydro-1-methyl-2-methylthio-4-oxopyrimidine (2 g.) was boiled with Raney nickel (10 g.; weighed wet) in water (30 ml.) for 1½ hr. Evaporation of the filtered solution, and extraction of the dry residue with boiling *iso*butyl methyl ketone (120 ml.), gave almost colourless needles (57%) of 1 : 4-*dihydro*-1-*methyl*-4-*oxopyrimidine*, m. p. 155—156° (Found: C, 54·1; H, 5·3; N, 25·45. $C_5H_6ON_2$ requires C, 54·5; H, 5·5; N, 25·45%).

3-*Methyluracil*.—1 : 6-Dihydro-1-methyl-2-methylthio-6-oxopyrimidine (0·97 g.) was refluxed for 1 hr. with hydrochloric acid (*d*, 1·1; 10 ml.), then evaporated to dryness *in vacuo*. Recrystallization from ethanol (6 parts) gave 83% of colourless 3-methyluracil, m. p. 179° (Found: N, 22·25%). It was also made (mixed m. p.) according to Whitehead (*loc. cit.*).

5 : 6-*Dihydro*-1-*methyluracil*.—Methyl β-methylaminopropionate (33 g.; Lindsay and Cheldelin, *J. Amer. Chem. Soc.*, 1950, **72**, 828) was dissolved in hydrochloric acid (1·0N; 295 ml.). Sodium cyanate (19 g.) was added and the solution refluxed for 24 hr. The water was distilled off (water-bath; 25 mm.) and the residue extracted with boiling ethyl acetate (2 × 350 ml.) (yield, 10 g.). Recrystallization from ethyl acetate (50 parts) gave colourless needles of 5 : 6-*dihydro*-1-*methyluracil*, m. p. 170—172° (Found: C, 46·9; H, 6·15; N, 22·0; O, 24·8. $C_5H_8O_2N_2$ requires C, 46·9; H, 6·3; N, 21·9; O, 24·95%).

5-*Bromo*-5 : 6-*dihydro*-1-*methyluracil*.—5 : 6-Dihydro-1-methyluracil (3·1 g.) and bromine (1·45 ml.) were refluxed in glacial acetic acid (45 ml.), for about 7 min. The residual oil, after evaporation *in vacuo* on the water-bath, was diluted with water (10 ml.) and brought to pH 5 with 10N-sodium hydroxide. After refrigeration the solid (4 g.) was filtered off and washed with ice-water. Recrystallized from ethanol (carbon), 5-*bromo*-5 : 6-*dihydro*-1-*methyluracil* was white (Found: C, 28·95; H, 3·2; N, 13·5; Br, 38·7. $C_5H_7O_2N_2Br$ requires C, 29·0; H, 3·4; N, 13·55; Br, 38·6%). It melted at 140—144° with loss of hydrogen bromide, and resolidified, remelting at about 226°.

1-*Methyluracil* (*Unambiguous Synthesis*).—5-Bromo-5 : 6-dihydro-1-methyluracil (0·6 g.) was plunged into a bath at 155—160°. It was removed 2 min. after resolidifying. The crude material was dissolved in water and neutralized, and, after evaporation to dryness, the residue was extracted with boiling *iso*butyl methyl ketone (15 ml.), the extract giving 1-methyluracil on cooling. The crude product was also brominated and nitrated, giving respectively 5-bromo-1-methyluracil (Found : C, 29·4; H, 2·65. Calc. for $C_5H_5O_2N_2Br$: C, 29·3; H, 2·45%) and 1-methyl-5-nitrouracil (Found : N, 24·6. Calc. for $C_5H_5O_4N_3$: N, 24·55%) (mixed m. p.s). The former, prepared from pure 1-methyluracil by bromination in water (Hilbert, *loc. cit.*) and recrystallized from water (50 parts), had m. p. 266° (decomp.).

3-Methyl-5-bromouracil, prepared as was the 1-methyl isomer and recrystallized from water (35 parts), had m. p. 228—229°, depressed strongly by authentic 1-methyl-5-bromouracil.

1-*Methyl-5-nitrouracil*.—Nitric acid (*d* 1·52; 0·25 ml.) was added to 1-methyluracil (0·5 g.) dissolved in concentrated sulphuric acid (1 ml.) at room temperature. After 20 min. the solution was poured on ice, giving 0·58 g. of 1-methyl-5-nitrouracil. Recrystallized from water (17 parts), it melted slowly with decomp. from 256° to 264°, according to rate of heating. It showed no depression with material prepared as above. Identical material was prepared by hydrolysis of 1-methyl-5-nitrocytosine (Johns, *J. Biol. Chem.*, 1912, **11**, 73).

3-Methyl-5-nitrouracil, prepared from 3-methyluracil (cf. the 1-methyl isomer) in 93% yield and crystallized from water, had m. p. 263—265° (decomp.), depressed by the 1-methyl isomer. Nitration at 100° according to Johnson and Heyl (*loc. cit.*) gave no nitro-derivative.

1 : 3-Dimethyl-5-nitrouracil (formerly prepared by methylation of nitrouracil or indirectly) when obtained from 1 : 3-dimethyluracil as above (80% yield) had m. p. 155° (decomp.).

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Stages in Oxidations of Organic Compounds by Potassium Permanganate. Part V. Oxidations of Some α-Hydroxy-acids by Manganic Pyrophosphate.*

By (Miss) P. Levesley and William A. Waters.

[Reprint Order No. 5686.]

Oxidation of α-hydroxy-acids by manganic pyrophosphate involves the reversible formation of a cyclic complex which then breaks down with loss of carbon dioxide and formation of a free radical. Further extensive oxidation follows, tartaric and malic acids being degraded to carbon dioxide and formic acid.

Manganous ions retard the rate of oxidation.

The kinetic investigations described by Drummond and Waters (Parts III and IV *) have now been extended to the manganic pyrophosphate oxidations of simple α-hydroxy-acids. Whilst (+)-tartaric, *meso*tartaric, and DL-malic acids have been studied more particularly, racemic, lactic, and glycollic acids have been examined sufficiently to show that they are oxidised by the same mechanism, and it has been shown that β-hydroxybutyric acid is hardly attacked.

In many respects the oxidations of tartaric and malic acids resemble that of pinacol (Part III), though the nature of its oxidation products and the absence of a comparable oxidation with dimethyl tartrate clearly show that tartaric acid does not behave merely

* Parts III and IV, *J.*, 1953, 3119; 1954, 2456.

as a 1 : 2-glycol. The initial reactions are strictly of first order with respect to $[Mn^{III}]$ (Table 2), and the variation of rate with respect to acid concentration can be expressed as $-d[Mn^{III}]/dt = k[Acid]/(a + [Acid])$ (Figs. 1 and 2; Tables 3—5). Again the oxidation rate is retarded to about half its value by the addition of vinyl cyanide, which polymerises. The free radicals which are formed can reduce mercuric chloride but do not combine with oxygen or promote oxidation of ethanol or *iso*propanol (contrast the oxidation of malonic acid; Part IV). However the rates of oxidation of the α-hydroxy-acids are retarded by the addition of manganous sulphate, according to the equation $1/(d[Mn^{III}]/dt) = k(1 + b)/[Mn^{II}]$ (Tables 6 and 7), though the extent of this retardation does not reach an upper limit, as noticed in the oxidation of pyruvic acid (Part VI, in the press).

In all cases the evolution of carbon dioxide sets in immediately and continues at a steady rate as the oxidation proceeds. This evolution of gas is not entirely eliminated by

FIG. 1.

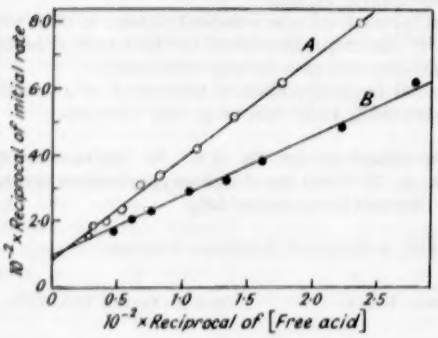


FIG. 2.

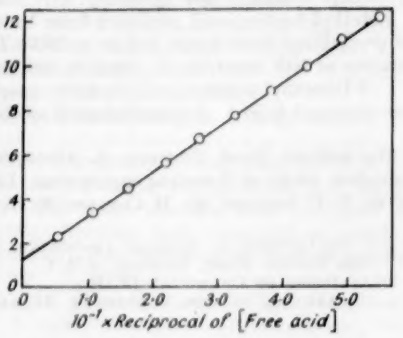


FIG. 1. *Oxidations of* (+)- *and of* meso-*tartaric acid.*

Reciprocal rate relations between oxidation rate and concentration of *free* organic acid. Initial $[Mn^{II}]$, $4{\cdot}9 \times 10^{-3}$M; [Pyrophosphate], 0·29M. Temp., 35°; pH, 1·9.

Line A. (+)-*Tartaric acid*: *initial* $[Mn^{III}]$, $1{\cdot}9 \times 10^{-2}$M.
Line B. meso*Tartaric acid*: *initial* $[Mn^{III}]$, $1{\cdot}82 \times 10^{-2}$M.

FIG. 2. *Oxidation of* DL-*malic acid.*

Reciprocal rate relation between oxidation rate and concentration of *free* malic acid. Initial $[Mn^{II}]$, $4{\cdot}9 \times 10^{-3}$M; initial $[Mn^{III}]$, $1{\cdot}80 \times 10^{-2}$M; [Pyrophosphate], 0·29M. Temp. 35°; pH, 1·9.

the addition of vinyl cyanide and consequently some carbon dioxide must be formed by the initial oxidation step. When oxidation is prolonged in the presence of an excess of manganic pyrophosphate very extensive oxidation occurs. Carbon dioxide and formic acid are formed from both tartaric and malic acid in amounts approximating to the equations:

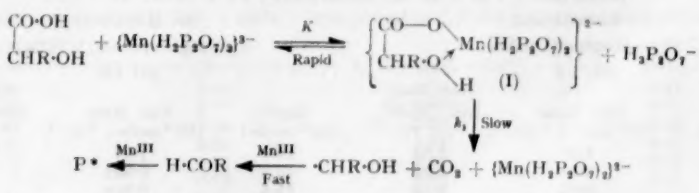
$$HO_2C{\cdot}[CH(OH)]_2{\cdot}CO_2H + 8Mn^{III} + 2H_2O = 3CO_2 + H{\cdot}CO_2H + 8Mn^{II} + 8H^+$$
(Found: 7·7 equiv. of Mn^{III}; ratio $CO_2/Mn^{III} = 3/7{\cdot}3$)

$$HO_2C{\cdot}CH(OH){\cdot}CH_2{\cdot}CO_2H + 10Mn^{III} + 3H_2O = 3CO_2 + H{\cdot}CO_2H + 10Mn^{II} + 10H^+$$
(Found: ratio $CO_2/Mn^{III} = 3/8{\cdot}9$)

whilst lactic acid consumes 7·1 equivalents of Mn^{III} per mole and so is not converted, *via* pyruvic acid, just into carbon dioxide and acetic acid (4 equiv. of Mn^{III}).

Except for the retardation due to manganous ions the kinetics of the oxidations of these α-hydroxy-acids are sufficiently similar to that of pinacol (*loc. cit.*) to indicate that a similar mechanism involving the fast, initial, reversible formation of a chelated manganic complex is involved, and indeed with tartaric acid the immediate change in colour of the solution

at pH 1—2 (pink ⟶ brown) clearly shows the occurrence of this complex formation. The general oxidation scheme is therefore considered to be as annexed.



From tartaric acid the final oxidation probably has the sequence :

$$HO_2C{\cdot}CH(OH){\cdot}CHO \longrightarrow HO{\cdot}CH(CO_2H)_2 \longrightarrow 2CO_2 + H{\cdot}CO_2H \text{ (cf. Part IV)}$$

and from malic acid :

$$HO_2C{\cdot}CH_2{\cdot}CHO \longrightarrow HO_2C{\cdot}CH(OH){\cdot}CHO \longrightarrow 2CO_2 + H{\cdot}CO_2H$$

For the initial rate of oxidation the above scheme would lead to the rate equation below, which satisfies the appropriate kinetic measurements,

$$\frac{1}{-\,d[Mn^{III}]/dt} = \frac{1}{nk_1[Mn^{III}]}\left(\frac{[(H_2P_2O_7)^{-2}]}{K[Acid]} + 1\right) \quad . \quad . \quad . \quad . \quad . \quad . \quad (A)$$

where $[Mn^{III}]$ = total manganic salt taken (moles), n = number of equivalents of Mn^{III} consumed rapidly per mole of hydroxy-acid (>2), [Acid] = concentration of *free* hydroxy-acid (moles), and $[H_2P_2O_7]$ = concentration of pyrophosphate *not* involved in complex formation (the salt is always present in large excess). The reaction scheme, and its derived equation (*A*), need modification however to account for the retarding action of added manganous salt. A possible explanation of this is the reversible formation of an organomanganous salt complex which reduces the amount of free acid in the solution, *i.e.* :

$$R{\cdot}CH(OH){\cdot}CO_2H + \{Mn(H_2P_2O_7)\}^{-2} \overset{K'}{\rightleftharpoons} \{Mn^{II}(HO{\cdot}CHR{\cdot}CO_2)_2(H_2P_2O_7)\}^{-} + (H_2P_2O_7)^{-}$$

(compare the formation of copper tartrate); for, provided that the equilibrium constant (K') for this reaction is small the addition of the manganous salt should reduce the amount of free hydroxy-acid in proportion to $1/(1 + K'[Mn^{II}])$.

Postulation that the initial oxidation step [manganic complex (I) ⟶ radical, R·CH(OH)·] may be reversible does not accord with the experimental observations. In the first place the kinetics of the oxidations of α-hydroxy-acids are not at all similar to those for malonic acid (Part IV), as the oxidation rate is decreased rather than increased by addition of vinyl cyanide, and in the second place the free radical formed has reducing, and not oxidising, properties.

By the use of equation (*A*) the values of $K/[H_2P_2O_7]$ in Table 1, indicative of the equilibrium constant for the formation of the manganic complex (I), and of nk_1, indicative of its rate of degradation, have been computed from the results shown in Figs. 1 and 2.

TABLE 1. *Oxidations of α-hydroxy-acids with manganic pyrophosphate.*

Temp., 35°; pH, 1·9; total pyrophosphate = 0·29M. Initial $[Mn^{II}] = 4{\cdot}9 \times 10^{-3}$M.

Acid	$K/[(H_2P_2O_7)]$ (M^{-1})	nk_1 ($hr.^{-1}$)
(+)-Tartaric	23	6·8
*meso*Tartaric	49	6·4
dl-Malic	6·3	4·4

Racemic acid was oxidised at exactly the same rate as (+)-tartaric acid. It can be seen that though *meso*tartaric acid is oxidised about twice as fast as (+)-tartaric acid almost the whole difference can be ascribed to the different equilibrium constant for the complex formation, whilst malic acid, which has one potential chelating group only, combines with Mn^{III} to much less than half the extent of the tartaric acids.

• P = Products of aldehyde oxidation (cf. *J.*, 1953, 440).

TABLE 2. *Variation of initial oxidation rate with initial* [Mn^{III}].

Initial [acid], $1{\cdot}90 \times 10^{-3}$M; initial [$Mn^{II}$], $4{\cdot}9 \times 10^{-3}$M; 35°.

(+)-Tartaric acid [Pyrophosphate], 0·29M pH, 1·9			DL-Malic acid [Pyrophosphate], 0·197M pH 1·6		
[Mn^{III}] (10^{-3} mole $l.^{-1}$)	Init. Rate (10^{-3} mole $l.^{-1}$ $hr.^{-1}$)	Init. Rate / Init. [Mn^{III}] (× 10)	[Mn^{III}] (10^{-3} mole $l.^{-1}$)	Init. Rate (10^{-3} mole $l.^{-1}$ $hr.^{-1}$)	Init. Rate / Init. [Mn^{III}] (× 10)
18·6	4·30	2·32	18·0	1·07	59·4
17·3	3·94	2·28	16·8	0·961	57·2
16·1	3·85	2·39	15·6	0·908	58·2
14·9	3·39	2·33	14·4	0·846	58·7
13·6	3·24	2·38	13·2	0·772	58·5
8·7	3·15	2·53	12·0	0·708	59·0
6·2	1·37	2·21	10·8	0·656	60·7
3·7	0·77	2·08	4·8	0·283	59·0

TABLE 3. *Data for the calculated results shown in Fig.* 1*A*. *Oxidation of (+)-tartaric acid.* pH, 1·9; *Temp.* 35°.

Initial concns.: [Mn^{III}] $1{\cdot}90 \times 10^{-3}$M; [$Mn^{II}$], $4{\cdot}9 \times 10^{-3}$M; [Pyrophosphate], 0·29M.

Init. total acid (10^{-3} mole $l.^{-1}$)	Free acid (calc.) (10^{-3} mole $l.^{-1}$)	Init. rate [10^{-3} mole (Mn^{III}) $l.^{-1}$ $hr.^{-1}$]	$1/(10^3 . \text{Rate})$	$1/[10^3 (\text{Free acid})]$
4·95	4·03	6·45	1·55	0·248
3·96	3·15	5·41	1·85	0·317
3·07	2·39	4·98	2·01	0·418
2·47	1·89	4·23	2·36	0·530
1·98	1·49	3·28	3·10	0·671
1·64	1·22	2·99	3·34	0·822
1·24	0·91	2·39	4·19	1·104
0·99	0·72	1·95	5·13	1·397
0·79	0·57	1·63	6·15	1·761
0·59	0·42	1·25	7·97	2·364

TABLE 4. *Data for the calculated results shown in Fig.* 1*B*. *Oxidation of meso-tartaric acid.* pH, 1·9; *temp.*, 35°.

Initial concns.: [Mn^{III}], $1{\cdot}82 \times 10^{-3}$M; [$Mn^{II}$], $4{\cdot}9 \times 10^{-3}$M; [Pyrophosphate], 0·29M.

Init. total acid (10^{-3} mole $l.^{-1}$)	Free acid (calc.) (10^{-3} mole $l.^{-1}$)	Init. rate [10^{-3} mole (Mn^{III}) $l.^{-1}$ $hr.^{-1}$]	$1/(10^3 . \text{Rate})$	$1/[10^3 (\text{Free acid})]$
2·98	2·12	5·74	1·74	0·47
2·38	1·64	4·88	2·05	0·61
1·96	1·32	4·31	2·32	0·76
1·49	0·96	3·44	2·91	1·04
1·19	0·75	3·08	3·25	1·33
0·99	0·62	2·62	3·82	1·61
0·74	0·45	2·08	4·82	2·22
0·59	0·36	1·62	6·17	2·78

TABLE 5. *Data for the calculated results shown in Fig.* 2. *Oxidation of* DL-*malic acid.* pH, 1·9; *temp.* 35°.

Initial concns.: [Mn^{III}], $1{\cdot}80 \times 10^{-3}$M; [$Mn^{II}$], $4{\cdot}9 \times 10^{-3}$M; [Pyrophosphate], 0·29M.

Init. total acid (10^{-3} mole $l.^{-1}$)	Free acid (calc.) (10^{-3} mole $l.^{-1}$)	Init. rate [10^{-3} mole (Mn^{III}) $l.^{-1}$ $hr.^{-1}$]	$1/(10^3 . \text{Rate})$	$1/[10 (\text{Free acid})]$
20·00	19·05	4·35	2·3	0·53
10·00	9·36	2·94	3·4	1·07
6·67	6·19	2·22	4·5	1·62
5·00	4·70	1·79	5·6	2·20
4·00	3·68	1·49	6·7	2·71
3·33	3·07	1·30	7·7	3·26
2·86	2·61	1·14	8·8	3·82
2·50	2·29	1·02	9·9	4·37
2·22	2·04	0·90	11·1	4·90
2·00	1·83	0·83	12·1	5·47

TABLE 6. *Variation of initial rate with initial* [Mn^{II}] *for the oxidation of* (+)-*tartaric acid.* pH, 1·9; *temp.* 35°.

Initial concns.: [Mn^{III}], $1{\cdot}90 \times 10^{-3}$M; [Pyrophosphate], 0·29M; [Tartaric acid], $9{\cdot}50 \times 10^{-3}$M.

Init. [Mn^{II}] (10^{-3} mole $l.^{-1}$)	Init. rate [10^{-3} mole (Mn^{III}) $l.^{-1}$ $hr.^{-1}$)]	$1/[10^{-3}$ (Init. rate)]	$\left(\frac{1}{\text{Rate}_s} - \frac{1}{\text{Rate}_0}\right) \cdot \frac{1}{10^4[Mn^{II}]}$
4·87	2·66	3·76	5·44
4·38	2·77	3·62	5·73
3·90	3·08	3·25	5·49
3·41	3·36	2·98	5·48
1·95	4·27	2·34	6·31
0·97	6·26	1·60	5·03
0·00	9·03	1·11	—

TABLE 7. *Variation of initial rate with initial* [Mn^{II}] *for the oxidation of* DL-*malic acid.* pH, 1·3; *temp.* 35°.

Initial concns.: [Mn^{III}], $1{\cdot}60 \times 10^{-3}$M; [Pyrophosphate], 0·175M; [Malic acid], $3{\cdot}12 \times 10^{-3}$M.

Init. [Mn^{II}] (10^{-3} mole $l.^{-1}$)	Init. rate [10^{-3} mole (Mn^{III}) $l.^{-1}$ $hr.^{-1}$)]	$1/[10^{-3}$ (Init. rate)]	$\left(\frac{1}{\text{Rate}_s} - \frac{1}{\text{Rate}_0}\right) \cdot \frac{1}{10^4[Mn^{II}]}$
7·99	1·11	9·01	5·32
7·19	1·17	8·55	5·27
6·39	1·23	8·13	5·27
5·59	1·29	7·75	5·35
4·79	1·37	7·30	5·30
3·99	1·45	6·90	5·36
3·19	1·53	6·54	5·58
2·39	1·62	6·17	5·90
0·00	2·10	4·76	—

The first column of Tables 6 and 7 gives the amount of manganous sulphate added to each reaction mixture.

EXPERIMENTAL

Materials.—Calcium *meso*tartrate, prepared from (+)-tartaric acid (*Org. Synth.*, Coll. Vol. I, 2nd Edn., p. 497), was treated with a slight excess of 4N-sulphuric acid and after filtration the strength of the free *meso*tartaric acid in the solution ($K_1 = 7{\cdot}8 \times 10^{-4}$; $K_2 = 1{\cdot}6 \times 10^{-5}$) was determined by alkali-titration with, successively, methyl-red (pK 5·1) and thymol-blue (pK 1·7). Small amounts of calcium salts were shown to have no effect on the oxidation rates.

Racemic acid (*op. cit.*) was crystallised from water; DL-malic acid, m. p. 128—129°, was crystallised from ethyl acetate; solutions of (+)-tartaric acid and of lactic acid were prepared from " AnalaR " materials.

Measurements.—The volumetric measurements were carried out as described in Part III; carbon dioxide evolution was measured in Warburg respirometers, solutions saturated with carbon dioxide being used. The induced polymerisations of vinyl cyanide and the reductions of mercuric chloride were conducted in Thunberg tubes (see *J.*, 1953, 2836). The results are tabulated.

Oxidation Products.—The chromotropic acid reaction (Feigl, " Spot Tests," Elsevier, Amsterdam, 1947, p. 395) was used to establish the formation of formic acid from both tartaric and malic acid.

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Properties of Periodate-oxidised Polysaccharides. Part V. Micro-determination of Molecular Weights of Sugar Osazones from Measurements of Ultra-violet-light Absorption.*

By Vincent C. Barry, Joan E. McCormick, and P. W. D. Mitchell.

[Reprint Order No. 5699.]

Light-absorption data for ten sugar osazones, ranging in molecular weight from that of glycerosazone to that of a disaccharide osazone, have been determined. The extinction curves are characterised by the existence of three maxima and by a constant value of ε at the absorption maximum of longest wave-length. This enables molecular weights to be determined with an error of less than ±2%. The light absorption spectra of sugar osazones and some related compounds are discussed.

The degradation of various periodate-oxidised polysaccharides by phenylhydrazine leads to the production of mixtures of osazones of different molecular weights which can be separated by adsorption chromatography (Part IV *). Identification of these osazones by melting-point determinations was frequently unreliable, and conversion into osotriazoles was generally impracticable with the small quantities of osazones available. We were therefore prompted to examine the possibility of their identification by spectrophotometric methods.

Engel (*J. Amer. Chem. Soc.*, 1935, **57**, 2419) reported light-absorptions for some osazones of various sugars and sugar derivatives, but did not give values for the molecular extinction coefficients. We have, therefore, repeated some of his determinations and extended the range of osazones examined. The extinction curves of sugar osazones are characterised by the existence of three regions of maximum absorption (I, 256 mμ; II, 308—314 mμ; III, 395—399 mμ) illustrated for glycerosazone in Fig. 1, and further by little variation in value of ε, especially in region III where the differences come within the limits of experimental error (Table 1, Nos. 1—10). We have thus the conditions required for spectrophotometric determination of molecular weights (cf. Strain, *J. Biol. Chem.*, 1938, **123**, 425; Cunningham, Dawson, and Spring, *J.*, 1951, 2305). The accuracy of the

Table 1.

		I		II		III	
No.		$\lambda_{max.}$ (mμ)	$\varepsilon_{max.}$	$\lambda_{max.}$ (mμ)	$\varepsilon_{max.}$	$\lambda_{max.}$ (mμ)	$\varepsilon_{max.}$
Osazones.							
1	Glycerose	256	19,280	308—310	9,970	395—397	20,430
2	Erythrose	256	19,620	309	10,300	397	20,420
3	Arabinose	256	19,100	309—311	10,450	393—397	20,270
4	Xylose	256	19,610	308—312	10,440	397	20,360
5	Rhamnose	256	19,470	309—312	10,480	396—397	20,240
6	Galactose	256	20,230	309—311	10,840	395—397	20,700
7	Glucose	256	19,950	308—312	10,560	395—398	20,310
8	Maltose	256—257	21,450	309—314	10,640	399	20,430
9	Lactose	256—257	20,670	309—313	11,170	396—399	20,330
10	Melibiose	256	18,510	310—312	10,660	393—395	20,100
Bisphenylhydrazones.							
11	Glyoxal	—	—	302—304	10,110	378	46,410
12	Methylglyoxal	—	—	302—304	11,950	364	46,250
13	Diacetyl	—	—	305	14,190	352	46,400
Osotriazoles.							
14	Diacetyl	274—275	19,310				
15	Glycerose	266—277	18,970				
16	Glucose	267—278	18,670				

* Part IV, Barry and Mitchell, *J.*, 1954, 4020.

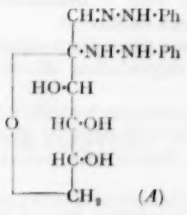
method is illustrated in Table 2 where the molecular weights of ten sugar osazones are calculated, by means of the average value, $\epsilon_{max.\ III} = 20{,}360$.

Included in Table 1 (Nos. 11—13) are light-absorption data for the "osazones" of glyoxal, methylglyoxal, and diacetyl which, as was pointed out by Engel (*loc. cit.*), differ markedly (see also Fig. 1) from those of the sugar osazones. (For this reason we think it preferable to name these compounds as bisphenylhydrazones.) Engel attributed this

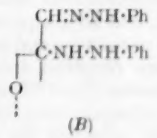
TABLE 2.

Osazone of:	c (mg./100 ml.)	$E_{max.}$	M, found	M, calc.	Error (%)
Glycerose	0·492	0·375	267	268	−0·4
Erythrose	0·486	0·333	297	298	−0·3
Arabinose	0·584	0·361	329	328	+0·3
Xylose	0·572	0·355	328	328	0
Rhamnose	0·620	0·367	344	342	+0·6
Galactose	0·614	0·355	352	358	−1·7
Glucose	0·610	0·346	359	358	+0·3
Maltose	0·606	0·238	518	520	−0·4
Lactose	0·596	0·233	521	520	+0·2
Melibiose	0·590	0·228	527	520	+1·3

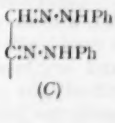
difference to the presence in the sugar osazones of an oxygen atom attached to $C_{(3)}$, whereas Percival and his co-workers have put forward evidence for the existence in glucosazone of a 2 : 6-oxide ring as in (*A*) (Summary in *Adv. Carbohydrate Chem.*, 1948, **3**, 29). While one should not be too rigid in the correlation of structure with ultra-violet-light absorption, one is tempted nevertheless to make a few observations regarding the relation between the structure of osazones and bisphenylhydrazones and their ultra-violet spectral absorption. Now the light-absorption properties of all the sugar osazones examined are closely similar, so, if one accepts an oxide ring structure for glucosazone, the same chromophoric grouping (*B*) must be present in each. Glycerosazone will then have a 2 : 3-oxide ring, and the tetrosazones and pentosazones presumably 2 : 4- and 2 : 5-oxide rings, respectively. Furthermore, in melibiosazone where $C_{(6)}$ of the reducing glucose residue is already involved in a glycosidic link, the oxide ring must again be different from that of glucosazone. The necessity for these varied assumptions, and Engel's positive evidence (*loc. cit.*) that 3 : 4 : 6-tri-*O*-methylglucosazone shows ultra-violet-light absorption closely similar to that of glucosazone, make it difficult to accept Percival's cyclic structure for glucosazone. Percival's case is based on his failure to prepare a methylated derivative of glucosazone containing a 6-methoxyl group, and he puts forward as additional evidence the findings of Diels, Cluss, Stephen, and König (*Ber.*, 1938, **71**, 1189) that triphenylmethyl chloride, a reagent which normally reacts readily with primary alcohol groups, does not react with glucosazone. We have no alternative explanation to offer of the lack of reactivity of the $CH_2{\cdot}OH$ group.



(*A*)



(*B*)



(*C*)

Percival suggests (*loc. cit.*) that in aqueous ethanolic solution an equilibrium is set up between the cyclic and acyclic modifications of glucosazone, such as is believed to obtain in solutions of the sugars themselves. The ultra-violet spectral absorption of glucosazone must then be due to the presence of the two chromophoric groupings, (*B*) and (*C*). Any variation in the proportions of the cyclic and acyclic modifications would be expected to show itself in altered ultra-violet absorption characteristics. As a result of the close

similarity of light absorption of all the sugar osazones, one would be thus compelled to postulate that the same equilibrium is reached in all cases. This would hardly be expected in view of the different structures involved, and it is evident that at the high dilutions used in the determination of ultra-violet absorption, the osazones are present only in the acyclic form.

The osotriazoles obtained from sugar osazones and diacetyl bisphenylhydrazone (Table 1, Nos. 14—16) show very similar light absorption (Fig. 2), indicating the absence in sugar osotriazoles of interaction between hydroxyl groups and the chromophore, such as obtains with osazones.

A satisfactory explanation of the apparently conflicting viewpoints referred to above must await more detailed investigation such as an extension of Percival's methylation

FIG. 1. FIG. 2.

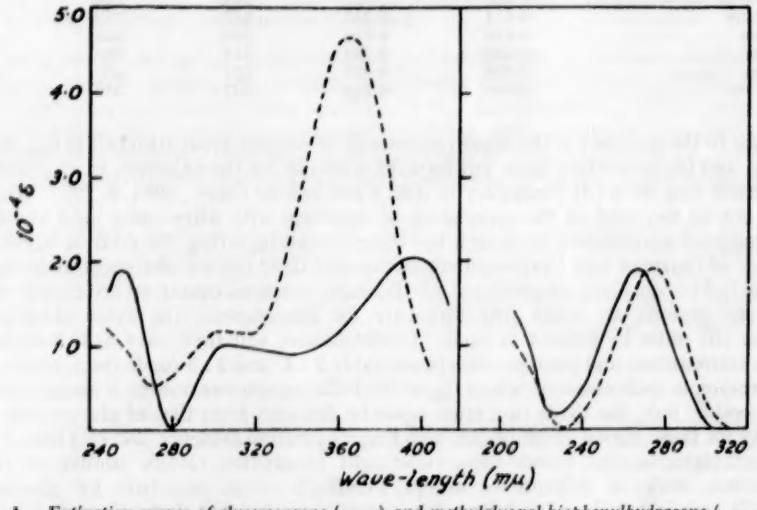


FIG. 1. *Extinction curves of glycerosazone* (——) *and methylglyoxal bisphenylhydrazone* (– – – –).
FIG. 2. *Extinction curves of the osotriazoles of glycerose* (——) *and diacetyl* (– – – –).

experiments to osazones of different molecular size. This might show whether in all these osazones a hydroxyl group is in fact involved in ring formation.

Experimental.—Light-absorption measurements were made with a Beckman Model DU spectrophotometer, a 1-cm. quartz cell, and 95% aqueous ethanol as solvent.

The osazones were prepared in the usual way and crystallised twice from aqueous ethanol. Glycerosazone and erythrosazone were obtained from the degradation of oxyinulin and oxystarch, respectively, by phenylhydrazine (Part IV, *loc. cit.*).

Glycerosotriazole was prepared by reduction with lithium aluminium hydride of 4-formyl-2-phenyl-2 : 1 : 3-triazole which is readily obtained by periodate oxidation of glucosotriazole. The product which was purified by adsorption on alumina and elution with benzene had m. p. 63—64°.

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Physicochemical Studies on Starches. Part II. The Oxidation of Starches by Potassium Metaperiodate.*

By D. M. W. Anderson, C. T. Greenwood, and E. L. Hirst.

[Reprint Order No. 5721.]

The oxidation of 18 different starches by potassium metaperiodate has been studied. At constant temperature, the time taken for the theoretical uptake of periodate ion varies from starch to starch. Only traces of glucose were found in the hydrolysates from oxidised starches when oxidation was continued until over-consumption of periodate had occurred. Potentiometric-titration studies showed that, in the presence of all reaction products, formic acid is quantitatively determined by titration to pH 6·25. Oxidised starches are stable below this pH, but decompose rapidly in dilute alkali, yielding acidic products in quantity. Oxidised starches bind about 2% of the formic acid released during oxidation; hence complete estimation of this acid can only be made by titrating the *heterogeneous* reaction mixture to pH 6·25. The effect of the presence of protein on the periodate oxidation of oat-starch samples has been investigated. Values for the ratio of non-terminal to terminal groups of the starches studied are presented, the accuracy claimed being ±0·5 glucose unit. The average length of unit-chain of the corresponding amylopectin components has been calculated from these values and the results of determinations of the percentages of amylose.

In recent years there has been an increasing tendency for the methylation method of determining the ratio of non-terminal to terminal groups [*i.e.*, $(\bar{R})$] in starches to be superseded by the method involving the estimation of formic acid released from the non-reducing end-groups during periodate oxidation. The periodate method has the advantages of simplicity and speed and requires about ten times less material. Theoretically, it can also provide additional evidence for the presence or absence of inter-chain linkages involving $C_{(2)}$ or $C_{(3)}$ (Halsall, Hirst, Jones, and Roudier, *Nature*, 1947, **160**, 899) and, in conjunction with methylation data, of glucose residues linked solely through $C_{(1)}$ and $C_{(6)}$ (Brown, Halsall, Hirst, and Jones, *J.*, 1948, 27). However, the accuracy of periodate determinations of the value of $(\bar{R})$ for starches has been quoted as ±10% (*idem*, *loc. cit.*). There has also been considerable disagreement in the values obtained for the average lengths of unit-chain of amylopectins by different workers (see Table 1). The studies reported here were undertaken in an effort to reduce the experimental errors

Table 1. *Values quoted from periodate oxidation results for the average length of unit chain of amylopectins.*

Source of starch	Reference A	B	C	D
Maize	20	—	25—26	25·2
Potato	24—26	—	27	—
Tapioca	20	22	23	26·6
Wheat	21	—	23	—

A, Brown, Halsall, Hirst and Jones, *loc. cit.*; B, Meyer and Settele, *Helv. Chim. Acta*, 1953, **36**, 197; C, Potter and Hassid, *J. Amer. Chem. Soc.*, 1948, **70**, 3488; D, *idem*, *ibid.*, 1951, **73**, 997.

involved in periodate oxidations, and so obtain accurate values of $(\bar{R})$ for use in conjunction with the results from differential potentiometric-titration studies of the iodine uptake of starches and their components.

Oxidations were carried out with potassium metaperiodate (Halsall, Hirst, and Jones, *J.*, 1947, 1399) at 15—16° and at 20—21°. At both temperatures, the time required for the theoretical uptake of 1·03—1·05 moles of periodate per anhydroglucose unit varied for

* Part I, *J.*, 1954, 3769.

different starches. Some typical results are shown in Table 2. In no case was the theoretical uptake reached in less than 240 hr. at 15—16°, and even after 350 hr. at this

TABLE 2. *Periodate uptake, in moles per anhydroglucose unit.*

		Time of oxidation (hours)							
Source of starch	Temp.	72	120	160	200	240	280	336	432
Barley I [a]	15—16°	—	—	0·91	0·99	1·01	1·04	—	—
Oat [b]	,,	0·77	0·80	0·86	0·96	1·02	—	1·05	—
Potato I [c]	,,	0·81	0·86	0·89	0·95	0·98	1·00	1·02	—
Potato II [d]	,,	—	—	0·88	0·94	0·96	—	1·01	1·04
Potato III [e]	,,	—	—	0·88	0·94	0·97	—	1·03	1·03
Rice [c]	,,	—	—	0·72	0·84	0·93	1·01	1·03	—
Sweet potato [c] ...	,,	—	—	—	0·97	1·01	—	—	—
Waxy maize [c]	,,	—	—	0·91	0·92	0·96	1·00	1·03	1·05
Oat [b]	20—21	—	0·97	1·02	1·03	—	1·08	—	—
Potato II [d]	,,	—	0·97	1·03	1·04	1·09	1·13	—	—
Rice [c]	,,	—	0·95	1·01	1·03	1·06	1·09	—	—
Waxy maize [c]	,,	—	0·98	1·02	—	1·03	1·05	—	—

[a] McWilliam and Percival, *J.*, 1951, 2259; [b] Anderson and Greenwood, unpublished work; [c] Samples described in *J.*, 1948, 27; [d] *Var.* "Golden Wonder"; [e] *Var.* "Redskin" ([d,e] Greenwood, unpublished work).

temperature, very little over-consumption of periodate (and hence very little over-oxidation of starch) occurs. At 20—21°, the oxidation is about 30% faster, but there is a greater tendency for over-oxidation.

It follows that the time required for the periodate-uptake of a starch to reach the theoretical value *at constant temperature* must be determined. The amount of formic acid liberated in a shorter time cannot be quantitative. Although a longer time may even be necessary to allow for hydrolysis of intermediate complexes (Hughes and Nevell, *Trans. Faraday Soc.*, 1948, **44**, 941), it has been found that in the final stages of oxidation the release of formic acid follows consumption of periodate without apparent delay (see Fig. 1). The differing oxidation times required could be explained by differences in chain length and degree of multiple branching of the amylopectin fractions, by differences in natural granular structure, or by alteration in the physical characteristics of the granules arising from differing methods of preparation. As a result, it appears unlikely that the oxidation time for any simple saccharide can be taken as a standard for starch. In particular, it is difficult to justify the procedure of Morrison, Kuyper, and Orten (*J. Amer. Chem. Soc.*, 1953, **75**, 1502), who apply a fixed correction factor, based on the percentage of the theoretical formic acid released in the same time from sucrose; results agreeing with those of Halsall, Hirst, and Jones (*J.*, 1947, 1427) have been obtained here which show that release of formic acid from sucrose is abnormally slow and non-quantitative. There is no reason to suspect that starches differ from the model of methyl β-D-maltoside (Brown, Halsall, Hirst, and Jones, *loc. cit.*) which releases formic acid quantitatively in 150 hr. at 15°, in any respect other than having variably slower rates of oxidation.

After several starches had been oxidised for the time found necessary for the theoretical uptake of periodate, they were examined by the methods described by Hirst, Jones, and Roudier (*J.*, 1948, 1779) for the isolation and hydrolysis of the oxidation products, and for the determination of glucose in the hydrolysates. Quantities of glucose between 0·5 and 1% were found. When further samples of the same starches were oxidised for at least 100 hr. longer in each case, traces of glucose, too small for estimation, were detectable only by examination of the chromatograms under ultra-violet light. Recent papers have reported the presence of 1—2% of glucose in hydrolysates after oxidation at room temperature for 240 hr. (Hirst, Jones, and Roudier, *loc. cit.*) and for 150 hr. (McWilliam and Percival, *loc. cit.*), but these authors were undecided whether this was of structural significance or due to incomplete oxidation. The latter explanation is supported by the present work, which shows that about 1% of glucose residues in the starches examined are abnormally but not completely resistant to periodate attack. This suggests that 1 : 2- or 1 : 3-glucosidic linkages are not present, and is in agreement with the work of Gibbons

and Boissonnas (*Helv. Chim. Acta*, 1950, **33**, 1477). However, the polyaldehydic oxidation products are very easily hydrolysed, giving solutions containing a brown precipitate, and Jackson and Hudson (*J. Amer. Chem. Soc.*, 1938, **60**, 989) reported that during hydrolysis some destruction of material occurred and polymer degradation was incomplete. For this reason, Abdel-Akher, Hamilton, Montgomery, and Smith (*ibid.*, 1952, **74**, 4970) hydrolysed the corresponding polyalcohols and claimed that 1 : 3-linkages exist since 1% of glucose residues was found. However, the period of oxidation used may not have been sufficient for complete oxidation.

The present work has shown that aqueous suspensions of the polyaldehydes obtained are stable in the range pH 3—6·25, but decompose readily in 0·01—0·001N-alkali, releasing acidic products even in a nitrogen atmosphere, with decomposition ceasing when the pH has dropped to 6·25. For example, immediately after potentiometric titration of a reaction mixture (Fig. 2, curve *abd*, of which part *bd* is time-dependent), the excess of alkali was back-titrated with standard formic acid (curve *dea*); 0·16 ml. of acid was found

FIG. 1.

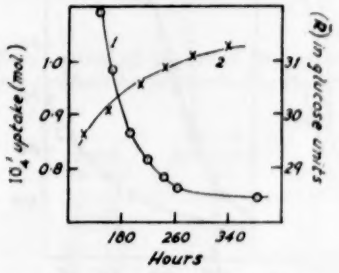

FIG. 2.

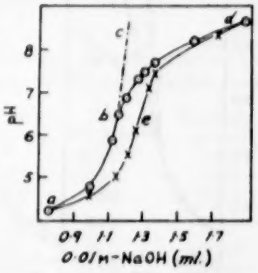

FIG. 1. *Variation of periodate-uptake and apparent value of R with oxidation time at 15—16° for oat starch.*

Curve 1. $(\bar{R})$ *(glucose units).*
Curve 2. IO_4'*-uptake (moles/anhydroglucose unit).*

FIG. 2. *Titration curves for a reaction mixture.*

Curve abc. Control $H{\cdot}CO_2H$–NaOH.
Curve abd. Reaction mixture–NaOH.
Curve dea. Back-titration curve for mixture–$H{\cdot}CO_2H$.

to have been liberated in the time taken (about 15 min.) to titrate from *b via d* to *e*. Liberation of acid in this manner may explain some anomalous results which have been reported involving over-production of acid during periodate oxidations in alkaline-buffered systems. Similarly, when a calculated excess of potassium hydroxide was added to a series of periodate oxidations of waxy maize starch at 15—16°, it was found that, although the rate of periodate uptake was normal (0·55 mole/162 g. of starch after 40 hr.), the acid liberated reached the theoretical value in only 38 hr. and continued to increase. The alkali-sensitivity of some aldehydes obtained by periodate oxidation has been investigated by Head (*J. Text. Inst.*, 1947, **38**, T 389), and it is considered that the acid formation reported here is due to alkaline hydrolysis of the acetal linkages accompanied by continued conversion of –CHO into $-CO_2H$ by Cannizzaro-type reactions and *not* to over-oxidation by periodate, as the uptake did not exceed 1·1 moles/anhydroglucose unit (cf. Barry, *J.*, 1942, 578).

There was the possibility that esterification of $C_{(6)}$ in the starch may occur with some of the liberated formic acid (cf. Gottlieb, Caldwell, and Hixon, *J. Amer. Chem. Soc.*, 1940, **62**, 3342; Tarkov and Stamm, *J. Phys. Chem.*, 1952, **56**, 262). This would account for the release of some acid when the oxidation product is treated with alkali, and would imply that the estimation of formic acid by titration of aliquot portions centrifuged free from

oxidised starch granules would not be quantitative. As esterification might have already occurred during preparation of the polyaldehydes, quantities were shaken for twelve days at 15—16° with concentrations of formic acid ten times greater than that normally released during oxidation, so that further esterification could occur. The formic acid was recovered quantitatively: in a similar experiment with pure starches, evidence of 0·2% removal of acid was obtained. Hence no significant quantity of formic acid becomes chemically bound as ester during periodate oxidations lasting 12 days at 15—16°.

As Halsall, Hirst, Jones, and Sansome (*Biochem. J.*, 1948, **43**, 70) have obtained evidence that different samples of the same starch, derived from plants differing in botanical variety and growth-conditions, contain the same proportions of end-group, and

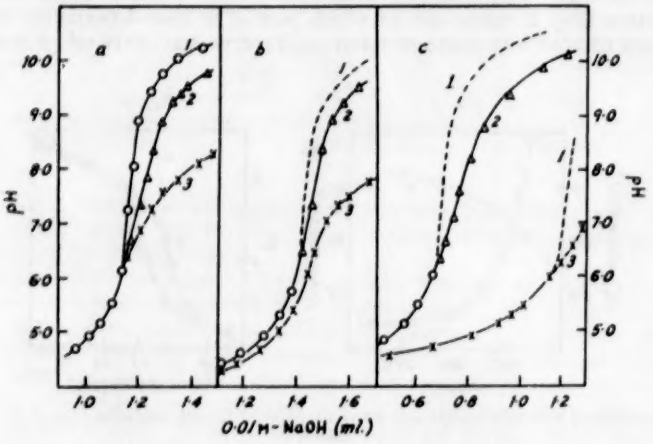

FIG. 3*a*. *Titration curves for control solutions.*

Curve 1. $H{\cdot}CO_2H$–NaOH.
Curve 2. ($H{\cdot}CO_2H$ + KCl + $NaIO_4$ + *ethylene glycol*)–NaOH.
Curve 3. [*As* (2) + *oxidised starch*]–NaOH.

FIG. 3*b*. *Titration curves for reaction mixtures.*

Curve 1. *Control* $H{\cdot}CO_2H$–NaOH.
Curve 2. *Centrifuged reaction mixture*–NaOH.
Curve 3. *Uncentrifuged reaction mixture*–NaOH.

FIG. 3*c*. *Titration curves for a proteinaceous reaction mixture.*

Curve 1. *Control* $H{\cdot}CO_2H$–NaOH.
Curve 2. *Centrifuged reaction mixture*–NaOH.
Curve 3. *Uncentrifuged reaction mixture*–NaOH.

as this result has been substantiated (see Table 3), the deviating periodate values in Table 1 could possibly be explained by experimental errors arising through incomplete oxidation and the use of differing procedures for the determination of formic acid. Abdel-Akher and F. Smith (*J. Amer. Chem. Soc.*, 1951, **73**, 994) prefer the iodometric method; Kerr and Cleveland (*ibid.*, 1952, **74**, 4036) titrate to pH 7·1, and papers in which titration to pH 5·5, 6·0, 8·0, and 8·2 was used have been referred to by Morrison, Kuyper, and Orten (*loc. cit.*), who showed that choice of end-point in the range pH 5·5—8·0 should have little influence on quantitative titration of *pure* formic acid. This is correct, but potentiometric titration studies carried out here, supported by iodometric determinations, have shown that quantitative titration of formic acid in the presence of all normal oxidation products is complete at pH 6·25, and that over-titration to pH 8·0 would reduce the value obtained for a true ($\bar{R}$) value of 25—30 by about 20%. In Fig. 3*a*, which shows typical potentiometric titration results for control solutions, the curve for pure formic acid (curve 1) differs

above pH 6·5 from that for the same quantity of acid in the equivalent of a centrifuged reaction mixture (curve 2). A still greater divergence occurs above pH 6·25 when 50 mg. of oxidised starch (carefully washed free from acid) are added, so giving the equivalent of an uncentrifuged reaction mixture (curve 3). Cori and Larner (*J. Biol. Chem.*, 1951, **188**, 17) noted " an apparent buffering action " during titration of periodate reaction mixtures : this is now explained by the alkaline degradation of oxidised starch. From the equivalence point of curve 1 at pH 7·1, it is seen that under these experimental conditions, titration of formic acid is complete by pH 6·5 for curve 2 and pH 6·25 for curve 3. The divergence of these curves above pH 6·25 is due to inclusion in the titration of substances other than formic acid.

Fig. 3 *b* shows the titration curves for a typical reaction mixture, curve 2 being for 10 ml. of centrifuged solution and curve 3 for 10 ml. of the heterogeneous mixture. Although both curves are superimposable with curve 1 for pure formic acid to pH 6·25, they are not themselves coincident over any range, and the end-points at pH 6·5 for (2) and pH 6·25 for 3 differ by 0·03 ml. Differences of this order (about 2% of the total titration) were consistently found. Investigation showed that the formic acid in the reaction mixture is not uniformly distributed, about 2% being loosely bound to the polyaldehydic

TABLE 3. *Average values of* $(\bar{R})$ *found for unfractionated starches, and calculated number of glucose residues per non-reducing end-group in the amylopectin fraction.*

Source of starch	Temp.	No. of determns.	Oxidation time (hr.) *	Av. value of $(\bar{R})$ †	Amylose ‡ content (%)	Calc. chain-length for amylopectin
Arrowroot [a]	15—16°	3	284—312	27·3	20·5	21·7
Banana [a]	15—16	2	244—336	26·3	16·8	21·9
Barley I [a]	15—16	4	260—282	29·5	22·0	23·0
Barley II [f]	15—16	2	260—282			
Iris germanica [g]	15—16	2	262—308	28·0	27·0	20·4
Maize [a]	15—16	2	300—384	26·5	24·0	20·1
Oat I and II [h]	15—16	5	240—318	27·4	26·0	20·3
	20—21	1	164—240			
Parsnip [h]	15—16	2	268—360	23·0	11·1	20·4
Pearl manioc [a]	15—16	2	244—312	24·1	15·7	20·3
Potato I [a]	15—16	2	291—383	28·3	20·4	22·5
Potato II [d]	15—16	2	336—455	28·3	21·0	22·4
	20—21	1	186			
Potato III [a]	15—16	2	335—455	28·3	21·0	22·4
Rice [a]	15—16	3	286—384	27·5	18·5	22·4
	20—21	1	164—212			
Sago [a]	15—16	2	244	25·0	26·0	18·5
Sweet potato [a]	15—16	2	266—310	28·2	17·8	23·2
Tapioca [a]	15—16	4	264—300	26·2	16·7	21·8
Waxy maize [a]	15—16	4	302—400	20·0	<1	20
	20—21	1	164—284			
Wheat [a]	15—16	4	260—306	26·2	25·0	19·6

* The time necessary (found by separate expt.) for periodate uptake to reach 1·03—1·05 moles/162 g. starch : the range quoted shows the period in which no over-oxidation occurred, the formic acid released being constant within the limits corresponding to $(\bar{R}) \pm 0·5$ glucose unit.

† All values obtained were within ±0·5 glucose unit from the average.

‡ Values obtained from potentiometric iodine titration curves (Anderson and Greenwood, unpublished work).

[a]–[g] See Table 1. [f] Aspinall, Hirst, and McArthur. [g] Aspinall and Johnstone. [h] Greenwood (all unpublished work).

oxidation product and removable by several washings with distilled water. Hence removal of the starch oxidation product before titration of formic acid gives values of $(\bar{R})$ which are about 0·5 glucose unit high. By careful titration of the heterogeneous reaction mixture to pH 6·25, any bound acid is included in the titre and there is no risk of including any acid arising from alkaline degradation of the polyaldehyde.

The behaviour of some protein-contaminated oat starches [obtained as intermediates in the purification of the pure starch (Anderson and Greenwood, unpublished work)] on

periodate oxidation has been studied. For protein contents of less than 3%, uptake of periodate is normal, and the correct value of $(\bar{R})$ is given when the sample weight is corrected for the percentage of protein present. The differences in titration curves of centrifuged and non-centrifuged samples increase with increasing protein-content. Fig. 3*c* shows the curves obtained for a product containing 23% of protein. The end-point for the centrifuged solution (pH 6·5; curve 2) gives a value of $(\bar{R})$ of 40, whilst that for the non-centrifuged solution (pH 6·25; curve 3) gives the correct value of $(\bar{R})$ of 28. Thus the presence of protein causes further complex-formation with formic acid, and the *heterogeneous* reaction mixture must be titrated. For samples containing more than 23% of protein, periodate uptake exceeds the theoretical value and no reliable estimate of $(\bar{R})$ can be obtained from the potentiometric-titration curves.

The potentiometric-titration method has been found to be the simplest and most reproducible for determining the formic acid released on periodate oxidation. Whilst the iodometric method, which determines total acidity, gives good agreement in determinations on pure starches, the potentiometric method has the advantage of showing from the shape of the titration curve whether acids other than formic are being titrated, so indicating the presence of impurity. The steam-distillation method has been found to give less consistent results for the small amounts of formic acid normally released, and it is slower.

The average values of $(\bar{R})$ found for the starches studied are presented in Table 3, the experimental error being within $\pm 0{\cdot}5$ glucose unit. The values deduced for the average length of unit-chain in the corresponding amylopectin components are also shown.

Under the experimental conditions described, periodate oxidation is a reliable and easy routine method for determining values of $(\bar{R})$ for starches, having an accuracy and reproducibility better than that of the methylation technique.

Experimental

All starch samples were dried *in vacuo* at 80° for several hours. Reagents were of analytical grade, or were purified as described by Halsall, Hirst, and Jones (*loc. cit.*). Nitrogen and sodium hydroxide used during potentiometric titrations were free from carbon dioxide.

Periodate Oxidations.—Starch (250—400 mg.) was suspended in 0·56M-potassium chloride (60 ml.) to which was added 0·2M-sodium metaperiodate (20 ml.). Within these limits the rate of oxidation was independent of the weight of starch. Reaction flasks were shaken continuously in the dark in a constant-temperature room.

Potentiometric Titrations.—Samples (10 ml.) were withdrawn by pipette at the required times. Ethylene glycol (1 ml.) was added and the mixture shaken in the dark for at least 10 min., the time found necessary for complete reaction between the glycol and the suspension of potassium periodate. (All excess of periodate *must be destroyed* before the start of a potentiometric titration.) Nitrogen was bubbled through the mixture for 10 min. before titration with 0·01M-sodium hydroxide (semimicro-burette). The passage of nitrogen was continued throughout the titration, which was followed by means of a glass electrode and Pye mains-operated pH-meter. Blank determinations showed that generally no correction was required for the acidity of the starch samples or of other reagents.

Withdrawal of samples by pipette whilst the reaction flask was *shaken gently* introduced no error. Each of seven 10-ml. portions withdrawn consecutively from a reaction mixture gave the same titre with sodium hydroxide, and, further, the value of $(\bar{R})$ deduced was the same as that obtained from titrations of the entire contents of each of three individual reaction mixtures (10 ml. each) after the same oxidation time. This procedure did not, however, give consistent results for determinations of excess of periodate as the more rapid sedimentation of potassium metaperiodate made impossible the withdrawal of samples homogeneous with respect to this component.

It was shown that no loss of acid occurred when nitrogen was passed through 0·0015M-formic acid for 1½ hr.

Oxidation of Formic Acid by Potassium Metaperiodate.—No loss of formic acid or consumption of periodate occurred when 0·0015M-formic acid was shaken with a saturated solution of potassium metaperiodate for 28 days in the dark at 15—16°. At 20—21°, however,

the concentrations of formic acid and of periodate decreased by 3% after 15 days, and by 6% after 21 days.

Distribution of Formic Acid in Reaction Mixtures.—After oxidation for 240 hr., a starch–potassium periodate reaction mixture (80 ml.) was divided into two. The first half was centrifuged, and portions (10 ml.) of the clear supernatant liquid were titrated (after destruction of excess of periodate) against 0·01024M-sodium hydroxide to pH 6·25. The average titre was 1·40 ml. From the second half, two *heterogeneous* 10-ml. portions were withdrawn, treated with glycol, and titrated to pH 6·25: the average titre was 1·43 ml. The remaining two 10-ml. portions were treated separately with glycol, then centrifuged, and the oxidised granules were washed three times with distilled water by centrifugation. The combined supernatant liquids and washings were then titrated to pH 6·25, the average titre being 1·43 ml.

Determination of Periodate Uptake.—Residual periodate concentration was determined by Fleury and Lange's indirect method (*J. Pharm. Chim.*, 1933, **17**, 107). This method gave satisfactory results in the presence of all reactants and products when the reaction mixture, to which had been added excess of bicarbonate, arsenite, and iodide, was *shaken in the dark for* 15 *min.* before back-titration with iodine. Periodate uptake was determined by analysis of a series of individual mixtures (10 ml., containing *ca.* 50 mg. of starch). The stoppers of the conical reaction flasks were lubricated with a little silicone grease.

Periodate Uptake and Formic Acid Release from Sucrose.—Results obtained (expressed in moles/mole of sucrose) were: (*a*) periodate uptake: 2·98 (262 hr.); 3·12 (300 hr.); (*b*) formic acid release: 0·87 (262 hr.); 0·88 (286 hr.); 0·89 (352 hr.); 0·91 (408 hr.); 0·92 (420 hr.); 0·93 (570 hr.).

Interaction of Formic Acid with Starches and their Oxidation Products.—The following mixtures were shaken for 240 hr. in the dark at 15—16°: (*a*) control solution of formic acid (10 ml.); (*b*) formic acid (10 ml.) and oat starch (64·35 mg.); (*c*) formic acid (10 ml.) and periodate-oxidised oat starch (65·18 mg.); (*d*) formic acid (10 ml.) and waxy maize starch (60·08 mg.); and (*e*) formic acid (10 ml.) and periodate-oxidised waxy maize starch (55·60 mg.). The contents of each reaction flask were then titrated to pH 6·25 against 0·00901M-sodium hydroxide, the titres obtained being (*a*) 16·15, (*b*) 16·05, (*c*) 16·15, (*d*) 15·85, and (*e*) 16·15 ml.

Examination of Polyaldehydic Oxidation Products.—No colour reaction occurred with (*a*) iodine–potassium iodide, (*b*) dilute sulphuric acid–potassium iodide, or (*c*) sulphuric acid–diphenylamine; Fehling's solution and Schiff's reagent were reduced. The release of acidic decomposition products from the oxidised starch in the presence of alkali was shown in the following experiments: (*a*) Oxidised oat starch (50 mg.) was added to water (5 ml.) which had been boiled, and then cooled, in the presence of nitrogen. 0·01024M-Sodium hydroxide (1 ml.) was added, and the mixture shaken for 15 hr. The pH was then 6·25, and did not decrease further during 24 hr. Further addition of 0·01024M-sodium hydroxide (1 ml.) gave an initial value of pH 10·5, which decreased overnight to pH 6·25 and did not decrease further. (*b*) Oxidised waxy maize starch (35·92 mg.) was shaken with 0·00901M-sodium hydroxide (20 ml.) for 17 hr. Titration of the excess of alkali to pH 6·25 required 1·70 ml. of 0·0147M-formic acid. Hence 232 g. of oxidised starch would liberate 1 l. of N-acid (duplicate experiment gave 273 g. as the apparent neutralisation equivalent).

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Polymers of Some Basic and Acidic α-Amino-acids.

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The preparation of polymers and copolymers of L-lysine, L-glutamic acid, and L-tyrosine is recorded.

The preparation of some polymers containing acidic and basic amino-acids, by standard and by modified methods, presented minor anomalies.

Digestion of poly(benzyl glutamate) (Hanby, Waley, and Watson, *J.*, 1950, **3239**) with hydrogen chloride–acetic acid for 8 hours at 60° (cf. Ben-Ishae and Berger, *J. Org. Chem.*, 1952, **17**, 1564) led to a product which dissolved in bicarbonate solution. Purification and analysis revealed, however, that the polymer was only partially debenzylated. An attempt was consequently made to prepare the γ-methylbenzyl esters of polyglutamic acid in the hope that such compounds might be more readily hydrolysed by the hydrochloric acid treatment. Only small yields of the *m*-methylbenzyl ester resulted when glutamic acid was esterified with *m*-tolylmethanol or when copper glutamate was treated with the appropriate halide (Hanby *et al.*, *loc. cit.*). No better results were obtained by using the *p*-methylbenzyl ester, which proved markedly unstable, decomposing on simple crystallisation. We, therefore, turned again to poly(benzyl glutamate) and found that when the material was suspended in hydrobromic–acetic acid dissolution slowly occurred followed by separation of poly-L-glutamic acid. Van Slyke analyses showed that no decrease in chain length or cyclisation of the *N*-terminal residue had taken place (cf. Hanby *et al.*, *loc. cit.*); racemisation was not observed.

Attempts to prepare poly-L-tyrosine from *ON*-dibenzyloxycarbonyl-L-tyrosine were not pursued as yields of the latter compound were poor. Reaction of tyrosine with one mol. of a cupric salt in the presence of exactly one mol. of alkali hydroxide (larger quantities caused precipitation of the complex) gave a soluble copper complex which afforded *O*-benzyloxycarbonyl-L-tyrosine in satisfactory yield (cf. Kurtz, *J. Biol. Chem.*, 1937, **122**, 477; 1949, **180**, 1253; Neuberger and Sanger, *Biochem. J.*, 1943, **37**, 515), and with carbonyl chloride in dioxan this gave the *N*-carboxyanhydride, smoothly converted into poly-(*O*-benzyloxycarbonyl-L-tyrosine). This polymer was insoluble in acetic acid and unaffected by hydrogen bromide–acetic acid at room temperature. At 50° the benzyloxycarbonyl group was removed without obvious dissolution of the material, to give a poly-L-tyrosine which was slightly discoloured. As the benzyloxycarbonyl-polypeptide was soluble in phenol, attempts were made to effect removal of the blocking group with hydrogen chloride in phenol at 60°; but the quality of the product was not improved.

Better results followed the use of acetyl as the protecting residue. *O*-Acetyl-*N*-benzyloxycarbonyl-L-tyrosine (Bergmann, Zervas, Salzmann, and Schleich, *Z. physiol. Chem.*, 1934, **124**, 22) was converted into *O*-acetyl-L-tyrosine *N*-carboxyanhydride by treatment with thionyl chloride in acetic anhydride (cf. Bailey, *J.*, 1950, 3461) and thence into poly-(*O*-acetyl-L-tyrosine). The last compound dissolved in hydrogen bromide–acetic acid at room temperature with separation, after *ca.* 5 hours, of poly-L-tyrosine, which was not discoloured. Its chain length, as shown by amino-nitrogen determinations, had not been affected by the hydrolytic treatment. The material differed from the poly-L-tyrosine described by Katchalski and Sela (*J. Amer. Chem. Soc.*, 1953, **75**, 5284) (see p. 235).

The benzyloxycarbonyl groups of poly-[1-ε-benzyloxycarbonyl-L-lysine : 1-(*O*-acetyl-L-tyrosine)] amide,* poly-[1-ε-benzyloxycarbonyl-L-lysine : 1-(γ-benzyl L-glutamate)] amide, and poly-[1-*O*-acetyl-L-tyrosine : 3-(γ-benzyl L-glutamate)], prepared *via* the *N*-carboxyanhydrides, were completely removed by hydrogen bromide–acetic acid at room temperature overnight. Poly-[1-*O*-acetyl-L-tyrosine : 1-(γ-benzyl L-glutamate)], after unmasking, was soluble

* The numeral before each component of the polymer indicates the presumed molar proportion of the component in the polymer.

only in caustic alkali : it was, consequently, impossible to show that complete deacetylation had been effected by the acid treatment; that this had occurred was, however, rendered likely by the observation that poly-[1-*O*-acetyl-L-tyrosine : 3-(γ-benzyl L-glutamate)] was fully deacetylated by similar treatment. Poly-(1-L-lysine : 1-L-tyrosine : 1-L-glutamic acid) proved to be completely soluble only in alkali hydroxide.

Copolymers of ε-benzyloxycarbonyl-L-lysine or γ-benzyl L-glutamate with L-cystine gave discoloured products on treatment with hydrogen bromide–acetic acid or with anhydrous hydrogen chloride. Poly-L-histidine could not be prepared. 1′-Benzyl-L-histidine failed to react with carbonyl chloride, whilst its α-benzyloxycarbonyl-derivative gave a crystalline product with phosphorus pentachloride that proved too unstable for identification.

Experimental

O-Benzyloxycarbonyl-L-tyrosine.—L-Tyrosine (9·0 g., 0·05 mol.) in N-sodium hydroxide (100 ml.; 0·1 mol.) was treated with copper sulphate pentahydrate (6·25 g., 0·025 mol.) in water (25 ml.), and the mixture stirred until the precipitated material had dissolved, then cooled in ice. Benzyl chloroformate (8·6 g., 0·05 mol.) was added in 3 portions during 20 min., with vigorous stirring, the copper benzyloxycarbonyl-complex being precipitated. Stirring was continued for a further 20 min., then the mixture was acidified with concentrated hydrochloric acid in order to dissolve the copper salts from the solids and was stirred for 2 hr., and the product was collected and recrystallised from acetic acid. The analytical sample was crystallised from hot water. *O-Benzyloxycarbonyl-L-tyrosine* had m. p. 215° (decomp.) (Found: C, 65·0; H, 5·4; N, 4·6. $C_{17}H_{17}O_5N$ requires C, 64·8; H, 5·4; N, 4·4%). It was converted into *O*-benzyloxycarbonyl-*N*-carboxy-L-tyrosine anhydride, m. p. 106° (decomp.). Katchalski and Sela (*loc. cit.*) give m. p. 101° (decomp.).

O-Acetyl-N-carboxy-L-tyrosine anhydride (cf. Farthing, *J.*, 1950, 3213).—*O*-Acetyl-*N*-benzyloxycarbonyl-L-tyrosine (8 g.) (Bergmann *et al.*, *loc. cit.*) was suspended in acetic anhydride (20 ml.), and thionyl chloride (11 ml.) added. The mixture was warmed to 40—50° and there maintained until dissolution was complete and effervescence had ceased, then cooled. Dry ether (20 ml.) and light petroleum (150 ml.; b. p. 40—60°) were added, the anhydride crystallising. The product (4·4 g., 79%) had m. p. 119—121° (decomp.) after two crystallisations from ethyl acetate–light petroleum. Bailey (*loc. cit.*) gives m. p. 120°.

Polymerisation of N-Carboxy-anhydrides.—(i) In dioxan (3·6 ml. per mol. of anhydride), 0·033 equiv. of ammonia in dioxan was used as initiator, with 16 hours' stirring at room temperature [cf. (*a*) Becker and Stahmann (*J. Amer. Chem. Soc.*, 1952, **74**, 38) whose work indicates that polymers of *ca.* 30 units chain length are formed under these conditions, (*b*) Sela and Berger (*ibid.*, 1953, **75**, 6350)]. One equiv. of 0·16N-hydrochloric acid was then added, the suspension stirred for 6 hr., and the polymer collected, washed with water, and dried *in vacuo*.

(ii) The amino-acid was refluxed overnight in boiling benzene saturated with water, then cooled, and the precipitated polymer was collected, washed with benzene and with ether, and dried *in vacuo*.

(iii) Polymerisation was effected in pyridine at room temperature for 6 days. After addition of ether the precipitated polymer was collected, washed with ether, and dried.

Chain-lengths, when given, are based on van Slyke amino-nitrogen analyses of the polymers obtained after removal of benzyloxycarbonyl-groups. With polymers containing lysine, the assumed chain lengths based on the ratio [anhydride : initiator] are given in parentheses.

Analytical figures for the polymers were seldom satisfactory (cf. Frankel, Cordova, and Breuer, *J.*, 1953, 1991), acetyl determinations being particularly bad.

Poly-(γ-benzyl L-Glutamate)$_{50}$ Amide.—γ-Benzyl *N*-carboxy-L-glutamic anhydride (11·10 g., 0·042 mol.) was polymerised in dioxan to give this *amide* (9·2 g., 100%) [Found: C, 65·1; H, 6·0; N, 6·3. $(C_{12}H_{12}O_3N)_{50}.NH_3$ requires C, 65·6; H, 6·0; N, 6·5%].

Poly-(γ-benzyl L-Glutamate)$_{35}$ Amide.—The same anhydride (5·0 g., 0·0189 mol.) in dioxan gave the *35-amide* (2·7 g., 65%) [Found: C, 64·9; H, 6·0; N, 7·2. $(C_{12}H_{13}O_3N)_{35}.NH_3$ requires C, 65·6; H, 6·0; N, 6·6%].

Poly-(O-benzyloxycarbonyl-L-tyrosine)$_{104}$.—This *polymer* was obtained (3·55 g., 92%) from the monomer (4·45 g., 0·013 mol.) in benzene (150 ml.) [Found: C, 68·2; H, 5·1; N, 4·9. $(C_{17}H_{15}O_4N)_{104}.H_2O$ requires C, 68·6; H, 5·0; N, 4·7%].

Poly-(O-acetyl-L-tyrosine)$_{70}$.—*O*-Acetyl-*N*-carboxy-L-tyrosine anhydride (3·68 g., 0·015 mol.)

was polymerised in benzene (90 ml.) to give the *poly*-(O-*acetyl*-L-*tyrosine*) (2·84 g., 94%) [Found: C, 63·2; H, 5·6; N, 7·2. $(C_{11}H_{11}O_3N)_{75}.H_2O$ requires C, 64·3; H, 5·4; N, 6·8%].

Poly-(O-*acetyl*-L-*tyrosine*)$_{33}$ *Amide*.—The anhydride (2·85 g., 0·011 mol.) was polymerised in dioxan, yielding this *amide* (1·34 g., 57%) [Found: C, 58·3; H, 5·7; N, 7·2; Ac, 27·0. $(C_{11}H_{11}O_3N)_{33}.NH_3$ requires C, 64·2; H, 5·4; N, 7·0; Ac, 20·9%].

Poly-(O-*acetyl*-L-*tyrosine*)$_{19}$.—The anhydride (3·35 g., 0·013 mol.) was polymerised in dioxan, giving the 19-*polymer* (1·6 g., 58%) [Found: C, 62·5; H, 5·6; N, 7·1; Ac, 24·3. $(C_{11}H_{11}O_3N)_{19}.H_2O$ requires C, 64·1; H, 5·4; N, 6·8; Ac, 20·9%].

Poly-[1-ε-*benzyloxycarbonyl*-L-*lysine*: 1-(γ-*Benzyl* L-*Glutamate*)]$_{30}$ *Amide* (*A*).—γ-Benzyl *N*-carboxy-L-glutamic anhydride (3·70 g., 0·014 mol.) and ε-benzyloxycarbonyl-*N*-carboxy-L-lysine anhydride (4·3 g., 0·014 mol.) in dioxan gave the *copolymer* (6·05 g., 89%) [Found: C, 63·9; H, 6·6; N, 9·0. $(C_{14}H_{18}O_3N_2.C_{12}H_{13}O_3N)_{15}.NH_3$ requires C, 64·7; H, 6·5; N, 8·9%].

Poly-(1-ε-*benzyloxycarbonyl*-L-*lysine*: 1-O-*Acetyl*-L-*tyrosine*)$_{30}$ *Amide* (*B*).—*O*-Acetyl-*N*-carboxy-L-tyrosine anhydride (3·63 g., 0·015 mol.) and ε-benzyloxycarbonyl-*N*-carboxy-L-lysine anhydride (4·46 g., 0·015 mol.) in dioxan yielded this 30-*polymer* (6·62 g., 97%) [Found: C, 63·0; H, 6·3; N, 9·1; OAc, 16·8. $(C_{14}H_{18}O_3N_2.C_{11}H_{11}O_3N)_{15}.NH_3$ requires C, 64·1; H, 6·3; N, 9·2; OAc, 9·2%].

Poly-[3-(γ-*benzyl* L-*glutamate*) : 1-*O*-*acetyl*-L-*tyrosine*]$_{49}$ *amide* (*C*) was obtained (9·05 g., 96%) from the ester anhydride (8·64 g., 0·032 mol.) and the foregoing tyrosine anhydride (2·72 g., 0·011 mol.) by copolymerisation in dioxan [Found: C, 64·5; H, 5·9; N, 6·9; Ac, 13·8. $(C_{12}H_{13}O_3N)_{37}.(C_{11}H_{11}O_3N)_{12}.NH_3$ requires C, 65·3; H, 5·9; N, 6·6; Ac, 5·0%].

Poly-[1-ε-*benzyloxycarbonyl*-L-*lysine* : 1-(γ-*benzyl* L-*glutamate*) : 1-O-*acetyl*-L-*tyrosine*]$_{30}$ *Amide* (*D*).—The foregoing components (4·69 g., 0·018 mol.; and 4·44 g., 0·018 mol., respectively), and ε-benzyloxycarbonyl-*N*-carboxy-L-lysine anhydride (5·45 g., 0·018 mol.) were copolymerised in dioxan, yielding this *polymer* (10·85 g., 89%) [Found: C, 63·6; H, 6·2; N, 8·5; Ac, 15·1. $(C_{14}H_{18}O_3N_2.C_{12}H_{13}O_3N.C_{11}H_{11}O_3N)_{10}.NH_3$ requires C, 64·5; H, 6·2; N, 8·3; Ac, 6·25%].

Removal of the Protective Groups.—The following procedure was used for all the polymers except one (see below). The polymer was suspended in glacial acetic acid (5 pt.) and warmed to 50°. Partial dissolution generally occurred, the insoluble fraction swelling so that it could be finely dispersed. The mixture was allowed to cool, dissolved polymer separating as a gel. Then hydrobromic acid in acetic acid (25 pt. of 50% w/v) was added. Dissolution occurred in 5—15 min., after which separation of solids began as follows: polyglutamic acid 1—2 hr.; polytyrosine 4—5 hr.; copolymers of lysine 10—20 min. No separation occurred with copolymers of glutamic acid or of tyrosine except when lysine was also present. Next morning excess of ether was added, and the precipitated material collected by centrifugation, or, if oily, by decantation, and was washed well with ether and dried *in vacuo* over potassium hydroxide.

The 104-polymer did not dissolve in acetic acid. Its suspension in hydrobromic–acetic acid (as above) was warmed at 50° for 4 hr.

During hydrogen bromide treatment of the 35- and of the 19-polymer, samples were periodically assayed for chain-length by van Slyke amino-nitrogen determination. No decrease in chain-length was observed.

Polymers were purified as indicated below.

Poly-L-*glutamic acid*. (i) The crude polymer (from 4·7 g.) was dissolved in 5% potassium hydrogen carbonate solution, charcoal was added, and the mixture filtered through a Sterimat. Acidification precipitated polyglutamic acid which was centrifuged off, and washed well with water containing a trace of hydrochloric acid, and finally with water. The *polymer* was not dialysed to remove salt, as earlier experiments showed that preparations had a tendency to dissolve on dialysis against tap-water. It was dried *in vacuo*, to yield poly-(L-glutamic acid)$_{50}$ amide, $[\alpha]_D^{25}$ −83·3° (*c*, 1·018 in 2% aqueous $KHCO_3$) [Found: C, 43·9; H, 6·0; N, 11·2; amino-N, 0·216. $(C_5H_7O_3N)_{50}.NH_3$ requires C, 46·4; H, 5·5; N, 11·0; amino-N, 0·216%].

A sample (0·2779 g.) of this polymer was hydrolysed for 6 hr. with boiling 46—48% hydrobromic acid (10 ml.). The solution was made up to 25 ml. with water, giving α_D^{25} +1·214° (4-dm. tube); the product had N (Kjeldahl) 1·147 mg./ml., hence $[\alpha]_D^{25}$ is +25·19°. L-Glutamic acid, given similar treatment, had $[\alpha]_D^{25}$ +24·52°.

(ii) The 35-polymer (0·75 g.), similarly treated, gave *poly*-(L-*glutamic acid*)$_{35}$ *amide* (0·24 g., 54%), $[\alpha]_D^{18}$ −90·5° (*c*, 1·026 in 2% aqueous $KHCO_3$) [Found: C, 44·7; H, 5·8; N, 9·4; amino-N, 0·311. $(C_5H_7O_3N)_{35}.NH_3$ requires C, 36·3; H, 5·5; N, 11·1; amino-N, 0·309%].

Poly-L-*tyrosine*.—(i) The crude benzyloxycarbonyl 104-polymer (3·2 g.) was dissolved in the minimum quantity of N-sodium hydroxide; the solution was immediately treated with charcoal, filtered through a Sterimat, and acidified with dilute hydrochloric acid. The precipitated poly-

mer was centrifuged off, suspended in water, and dialysed against tap-water and finally against distilled water. *Poly*-(L-*tyrosine*)$_{104}$ (730 mg., 42%) was collected by centrifugation and dried *in vacuo*, having $[\alpha]_D^{26}$ +40·9° (*c*, 1·056 in N-NaOH) [Found: C, 63·6; H, 5·9; N, 8·0; amino-N, 0·083. $(C_9H_9O_2N)_{104},H_2O$ requires C, 66·2; H, 5·6; N, 8·6; amino-N, 0·082%].

(ii) The acetyl 79-polymer (2·84 g.) yielded *poly*-(L-*tyrosine*)$_{79}$ (1·0 g., 44%), $[\alpha]_D^{28}$ +32·2° (*c*, 1·014 in N-NaOH) [Found: C, 63·8; H, 5·8; N, 8·1; amino-N, 0·109. $(C_9H_9O_2N)_{79},H_2O$ requires C, 66·1; H, 5·6; N, 8·6; amino-N, 0·109%].

(iii) The acetyl 32-polymer (1·0 g.) yielded *poly*-(L-*tyrosine*)$_{32}$ *amide* (0·4 g., 50%), $[\alpha]_D^{26}$ +33·9° (*c*, 1·02 in N-NaOH) [Found: C, 60·7; H, 5·6; N, 7·4; amino-N, 0·265. $(C_9H_9O_2N)_{32},NH_3$ requires C, 66·0; H, 5·6; N, 8·8; amino-N, 0·267%].

(iv) The acetyl 19-polymer (0·65 g.) gave *poly*-(L-*tyrosine*)$_{19}$ (350 mg., 68%), $[\alpha]_D^{26}$ +17·8° (*c*, 1·01 in N-NaOH) [Found: C, 64·1; H, 5·7; N, 9·0; amino-N, 0·445. $(C_9H_9O_2N)_{19},H_2O$ requires C, 65·9; H, 5·6; N, 8·5; amino-N, 0·449%]. A sample (0·2535 g.) of poly-(L-tyrosine)$_{79}$ was hydrolysed under reflux for 28 hr. with 46—48% hydrobromic acid (15 ml.). The solution was filtered from a trace of insoluble matter and made up to 25 ml. with water. The product had $[\alpha]_D^{23}$ −0·072° (1-dm. tube), and N (Kjeldahl) 0·731 mg./ml., hence $[\alpha]_D^{23}$ −7·6°. L-Tyrosine, given similar treatment, had $[\alpha]_D^{25}$ −7·0°.

All rotations quoted for polytyrosine samples were read 20 min. after the solutions had been made up. It was found that rotations in N-sodium hydroxide at room temperature fell by *ca.* 10% after 5 hr., by 20% after 12 hr., and by 50% after 40 hr.

There is an indication from the values quoted above that rotation varies with chain length. Katchalski and Sela (*loc. cit.*), however, quote $[\alpha]_D^{20}$ +8·7° for a 75-polymer. They list a variety of solvents for this polytyrosine preparation. Our own preparations, in contrast, proved only partly soluble in these, dissolving completely only in caustic alkali.

Poly-[1-L-*lysine hydrobromide*: 1-(L-*glutamic acid*)]$_{30}$ *Amide*.—The crude polymer, obtained by hydrogen bromide treatment (of 4·9 g.), was dissolved in the minimum quantity of water and reprecipitated with excess of ethanol. It was collected and washed thoroughly with alcohol and then with ether. After being dried *in vacuo* the *polymer* (2·5 g., 73%) was dissolved in water, the solution was treated with charcoal, filtered through a Sterimat, and freeze-dried; the product had $[\alpha]_D^{15}$ −37·9° (*c*, 1·012 in H_2O) [Found: C, 37·6; H, 6·6; N, 9·7; Br, 24·7; amino-N, 3·9. $(C_6H_{13}ON_2Br,C_5H_7O_3N)_{15},NH_4Br$ requires C, 38·3; H, 5·9; N, 12·5; Br, 24·7; amino-N, 4·3%].

A solution of the polymer was titrated electrometrically against 0·089N-sodium hydroxide. A smooth sigmoid curve was obtained with neutralisation point at pH 7·2 (CO_2H: found, 13·5; calc., 13·1%).

Poly-(1-L-*lysine hydrobromide*: 1-L-*tyrosine*)$_{30}$ *Amide*.—The crude polymer obtained by hydrogen bromide treatment of the copolymer (B) (5 g.) was purified as for the copolymer (A), giving a *product* (6·62 g., 60%), $[\alpha]_D^{23}$ −19·5° (*c*, 1·046 in H_2O) [Found: C, 38·1; H, 5·6; N, 10·7; Br, 25·5; amino-N, 3·42; Ac, 0. $(C_6H_{13}ON_2Br,C_9H_9O_2N)_{15},NH_4Br$ requires C, 47·6; H, 5·9; N, 11·3; Br, 22·5; amino-N, 3·94%].

Electrometric titration of the polymer with 0·089N-sodium hydroxide did not give a smooth curve, precipitation occurring during the pH range 7·5—10·5. Ultra-violet absorption measurements gave tyrosine residue 31·4 (required 43·1%). It would thus appear that fractionation of the polymer occurred during purification, to give material with the constitution poly-(19-L-lysine hydrobromide: 11-L-tyrosine)$_{30}$ amide (Required: C, 43·7; H, 6·0; N, 11·9; Br, 27·2%).

Poly-[3-(L-*glutamic acid*): 1-L-*tyrosine*)$_{49}$ *Amide*.—The crude polymer from hydrogen bromide treatment of the copolymer (C) (8·05 g.) was dissolved in 5% potassium hydrogen carbonate solution (100 ml.) and the solution was treated with charcoal, filtered through a Sterimat, and acidified with dilute hydrochloric acid. The precipitated *product* (2·44 g., 47%) was collected, washed well with water, and dried *in vacuo*, then having $[\alpha]_D^{25}$ −40·6° (*c*, 1·014 in 2% aqueous $KHCO_3$) [Found: C, 48·9; H, 5·5; N, 10·3; amino-N, 0·209; Ac, 0·0 $(C_9H_9O_2N)_{12},(C_5H_7O_3N)_{37},NH_3$ requires C, 52·1; H, 5·8; N, 10·3; amino-N, 0·207%]. Ultra-violet absorption measurements gave a tyrosine residue content of 31·8% (required 29·5%).

Poly-[1-L-*lysine*: 1-(L-*glutamic acid*): 1-L-*tyrosine*)$_{20}$ *Amide*.—The crude polymer from hydrogen bromide treatment of the copolymer (D) (9·0 g.) was dissolved by adding N-sodium hydroxide (35 ml.) to its suspension in water (200 ml.). After treatment with charcoal, the mixture was filtered through a Sterimat and adjusted to pH 5 by hydrobromic acid. The precipitated polymer was collected by centrifugation, washed with water, 75% ethanol, and absolute ethanol, and finally dried *in vacuo* to give a partial *hydrobromide* (3·3 g., 50%), $[\alpha]_D^{20}$

$-35{\cdot}7°$ (*c*, 1·016 in N-NaOH) [Found: C, 53·2; H, 7·3; N, 11·2; Br, 4·2; Ac, 0. $(C_6H_{13}ON_3,C_8H_7O_3N,C_9H_9O_3N)_{10},NH_3,Br_{2\cdot3}$ requires C, 54·4; H, 6·7; N, 13·0; Br, 4·2%]. Tyrosine residue (by ultra-violet spectra) 35·6% (required 36·9%).

1'-Benzyl-α-benzyloxycarbonyl-L-histidine.—1'-Benzyl-L-histidine (1·85 g., 0·0075 mol.) (Du Vigneaud and Behrens, *J. Biol. Chem.*, 1937, **117**, 27), dissolved in N-sodium hydroxide (7·5 ml.), was treated at 0° with benzyl chloroformate (1·3 g., 0·0075 mol.) and N-sodium hydroxide (7·5 ml.) during 20 min. with stirring; a white precipitate separated. After 30 min. the mixture was acidified and the *1'-benzyl-α-benzyloxycarbonyl-L-histidine* (1·9 g., 66%) collected; it had m. p. 216° (decomp.) after crystallisation from pyridine (Found: C, 66·3; H, 5·4; N, 11·3. $C_{21}H_{21}O_4N_3$ requires C, 66·5; H, 5·6; N, 11·1%).

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Mesomorphism and Chemical Constitution. Part IV. The Effect of Substitution on the Mesomorphism of the* 6-n-*Alkoxy*-2-*naphthoic Acids.*

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Certain 6-*n*-alkoxy-5-halogeno- and -5-nitro-2-naphthoic acids have been prepared and their mesomorphic properties determined. The most stable mesophases are found in the 5-chloro-series and, as the size of the halogen substituent increases, the stability of the mesophases decreases. Despite the large dipole of the nitro-group, the 5-nitro-derivatives have the lowest mesomorphic thermal stability of the 5-substituted compounds which have been examined. These results are discussed with particular reference to the behaviour of the substituted series in relation to the parent 6-*n*-alkoxy-2-naphthoic acids.

IN Part III * the effect of halogen substitution on the mesomorphism of the 4-alkoxybenzoic acids was examined and in particular the mesomorphic behaviour of the 4-alkoxy-3-fluoro- and -3-chloro-benzoic acids was compared with that of the unsubstituted 4-alkoxybenzoic acids. When comparing the mesomorphic behaviour of two compounds, the temperature of transition of the mesophase to the isotropic liquid may be used as an indication of the relative stability of the two mesophases, although, for any one compound, the mesomorphic–isotropic transition temperature cannot be taken as a measure of the absolute stability of the mesophase. The true stability of a compound's mesophase would be obtained only by thermodynamic reasoning. In the above case the relative mesomorphic stability was found to decrease with increasing size of the halogen substituent. The study of the effect of substitution on mesomorphic stability has now been extended to the 6-*n*-alkoxy-5-chloro-, -bromo-, -iodo-, and -nitro-2-naphthoic acids, whose mesomorphic stabilities have been compared with those of the unsubstituted 6-alkoxy-2-naphthoic acids (Gray and Brynmor Jones, *J.*, 1954, 683). A qualitative comparison of the effect of substitution on the benzoic and naphthoic acids shows a pronounced difference. For instance, all the 6-alkoxy-5-halogeno-2-naphthoic acids possess considerable mesomorphic stability, whereas in the benzoic acids only 4-alkoxy-3-chloro- and -3-fluoro-benzoic acids exhibit mesomorphism, and the 3-bromo-acids are non-mesomorphic. Such behaviour reflects in part the greater thermal stability of the mesophases of the naphthoic acids (Gray and Brynmor Jones, *loc. cit.*).

The transition temperatures (solid–smectic and nematic, smectic–nematic and isotropic, and nematic–isotropic) of the series of naphthoic acids are tabulated below (the monotropic

* Part III, *J.*, 1954, 2556.

transitions and phase lengths are in parentheses). The smooth-curve relationships which have been found to be a feature of homologous series of mesomorphic compounds are again observed (Figs. 1—4) when the transition temperatures (the upper transition points and the smectic–nematic transitions) are plotted against the number of carbon atoms in the alkyl chain. In the nitro-series, because mesomorphic behaviour does not appear until the nonyl ether, only a selected few of the lower ethers were prepared. In the Table of results for the nitro-compounds no phase lengths have been included, since all the effects are monotropic.

Alkyl group	Temp. of transition to smectic	nematic	isotropic	Phase length of smectic	nematic
		6-Alkoxy-5-chloro-2-naphthoic acids			
Methyl	—	—	320·5°	—	—
Ethyl	—	—	269	—	—
Propyl	—	(217°)	220·5	—	(3·5°)
Butyl	—	209·5	216·5	—	7
Pentyl	—	189	208	—	19
Hexyl	(160·5°)	163·5	207	(3°)	43·5
Heptyl	165·5	176·5	201	11	24·5
Octyl	169	183	199	14	16
Nonyl	169	185·5	194·5	16·5	9
Decyl	167	186·5	192·5	19·5	6
Dodecyl	152	185·5	187·5	33·5	2
Hexadecyl	142·5	—	178·5	36	—
Octadecyl	138·5	—	174·5	36	—
		6-Alkoxy-5-bromo-2-naphthoic acids			
Methyl	—	—	303° (d)	—	—
Ethyl	—	—	281 (d)	—	—
Propyl	—	(<220·5°)	224	—	(>3·5°)
Butyl	—	(213)	214·5	—	(1·5)
Pentyl	—	196·5	207	—	10·5
Hexyl	—	178	203·5	—	25·5
Heptyl	158°	162	199	4°	37
Octyl	164	174·5	196	10·5	21·5
Nonyl	168	180	192·5	12	12·5
Decyl	167	182·5	189·5	15·5	7
Dodecyl	151·5	182	183·5	30·5	1·5
Hexadecyl	138·5	—	173·5	35	—
Octadecyl	136·5	—	169·5	33	—
		6-Alkoxy-5-iodo-2-naphthoic acids			
Methyl	—	—	296·5° (d)	—	—
Ethyl	—	—	286·5	—	—
Propyl	—	—	230	—	—
Butyl	—	(<208·5°)	219	—	(>10·5°)
Pentyl	—	(198)	204	—	(6)
Hexyl	—	191	195	—	4
Heptyl	—	176	189	—	13
Octyl	(<144°)	161·5	185·5	(>17·5)	24
Nonyl	(157·5)	163	182	(5·5)	19
Decyl	(164·5)	165	178·5	(0·5)	13·5
Dodecyl	146·5	169	172	22·5	3
Hexadecyl	133·5	—	165	31·5	—
Octadecyl	127	—	163	36	—

6-Alkoxy-5-nitro-2-naphthoic acids

Alkyl group	Temp. of transition to smectic I	smectic II	isotropic	Alkyl group	Temp. of transition to smectic I	smectic II	isotropic
Methyl	—	—	302°	Decyl	—	(166·5°)	175°
Pentyl	—	—	211	Dodecyl	(<162°)	(167)	173·5
Octyl	—	—	187	Hexadecyl	(<157)	(161)	163·5
Nonyl	—	(<159°)	173·5	Octadecyl	(<154)	(157·5)	162

In the 6-alkoxy-5-chloro-2-naphthoic acids (Fig. 1), the first phase (monotropic nematic) is shown by the propyl ether, and smectic properties are first introduced with a monotropic phase in the hexyl ether. In the 5-bromo-series also (Fig. 2) nematic properties

first appear at the propyl ether and the phase is monotropic, but, in this case, the isotropic liquid crystallised when it cooled slowly, and no accurate value could be obtained for the reversal to the mesophase. This phase is therefore seen only on cooling the isotropic liquid rapidly. The butyl ether too is monotropic in its nematic behaviour. Smectic properties now appear one unit later, at the heptyl ether. The onset of nematic properties in the 5-iodo-series (Fig. 3) occurs in the butyl ether and smectic properties do not appear until the octyl ether which, like the nonyl and the decyl ether, exhibits a monotropic phase. Such differences in the three series have only a qualitative significance, since the point at which a series first exhibits mesomorphism is dependent upon the relative values of the m. p. and the mesomorphic transition, and on the ability of the isotropic liquid to exist in a supercooled condition. The three 5-halogeno-series are, however, similar in that their hexadecyl and octadecyl ethers are purely smectic, and that their nematic– and smectic–isotropic transitions lie on smooth curves. In each series, the points for those ethers with an even number of carbon atoms in the alkyl chain lie on the upper curve, and those with an odd number on the lower curve. The smectic–nematic transitions also lie on smooth curves, which become coincident with the curve through the upper transition points for even-carbon-chain ethers. The only smectic–nematic transition which could not be determined was that for 5-iodo-6-*n*-octyloxy-2-naphthoic acid. Normally the nematic melt crystallises but, when the cooling was very rapid, the monotropic smectic phase was observed. In general character the three series are similar to the 6-alkoxy-2-naphthoic acids (Gray and Brynmor Jones, *loc. cit.*). Here again, the lower ethers are purely nematic, the nematic properties decrease and the smectic properties increase as the chain length grows, the hexadecyl and octadecyl ethers are purely smectic, and the smectic–nematic, and smectic– and nematic–isotropic transitions fall on curves.

The 6-alkoxy-5-nitro-2-naphthoic acids (Fig. 4) show a completely different behaviour. No mesophases are observed until the nonyl ether, which exhibits a monotropic phase, and this only when the isotropic liquid is rapidly chilled. In consequence, the transition temperature could not be obtained, nor could the texture of the phase be determined because of the rapid appearance of the crystals. It was, however, observed that the phase appears from the isotropic liquid in elongated particles, which are probably bâtonnets. The decyl ether behaves similarly, but here the temperature of reversal to the monotropic phase was easily determined, and the anisotropic particles coalesced and became homœotropic with positive uniaxial properties. The true nature of these elongated particles is very difficult to establish because of their transient existence before becoming homœotropic. The transition temperature of reversal to this monotropic, homœotropic phase, which is probably smectic, the possible existence of bâtonnets, and the positive uniaxial character of the phase were also established for the dodecyl, hexadecyl, and octadecyl ethers. However, these three ethers exhibit an additional phase which, when observed with the unaided eye, passes across the homœotropic phase (smectic II) as a well-defined wave front, succeeded rapidly by crystals. Since the first phase to appear from the isotropic liquid appears to be smectic (smectic II), the second phase occurring at a lower temperature must also be smectic (smectic I), and not nematic, because in all known cases in which smectic and nematic properties occur in the same compound, the nematic phase exists at the higher temperature. Further, the phases (smectic I) are anisotropic and, by rapid chilling, their appearances were easily examined under a microscope. They were found to consist of minute focal-conic groups, but in no case was it possible to determine the smectic II–smectic I transition temperature. These ethers therefore seem to provide further examples of polymesomorphism (Vorländer, *Trans. Faraday Soc.*, **1933**, **29**, 913; Bernal and Crowfoot, *ibid.*, p. 1032), which requires the existence in one compound of two phases of the same type but of different characteristic texture or appearance. This does not imply two individual structural types of the same phase, but rather that two different orientations of the same layer structure to the glass surface can give rise to two different appearances of the phase. Apart from this, there is further evidence for regarding phase II as smectic—the trend of the smectic–isotropic transition points when these are plotted against the number of carbon atoms in the alkyl chain (Fig. 4). These points lie on a curve which rises to a maximum and then falls to the hexadecyl and octadecyl ethers, and is quite unlike the

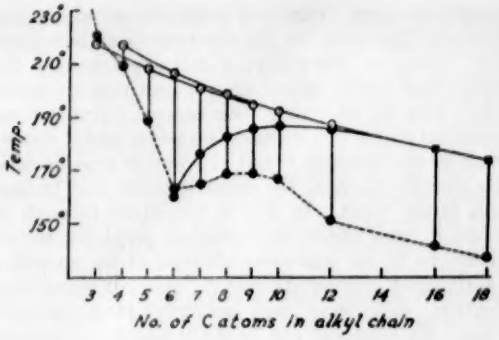


FIG. 1. *6-Alkoxy-5-chloro-2-naphthoic acids.*

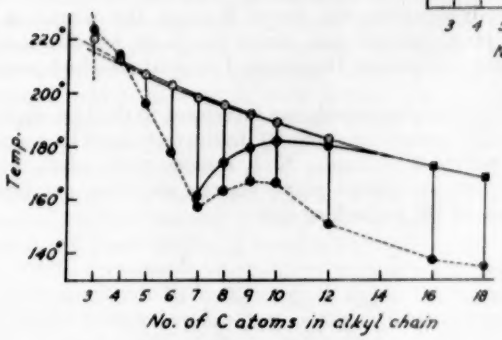


FIG. 2. *6-Alkoxy-5-bromo-2-naphthoic acids.*

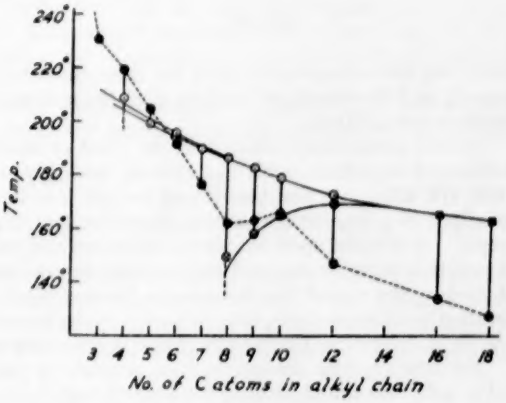


FIG. 3. *6-Alkoxy-5-iodo-2-naphthoic acids.*

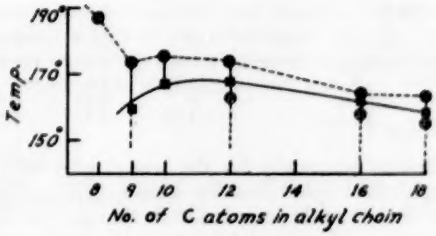
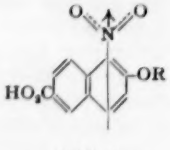


FIG. 4. *6-Alkoxy-5-nitro-2-naphthoic acids.*

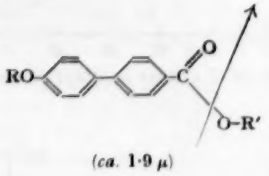
- ● *Solid–mesophase or isotropic liquid.*
- ⊗ *Smectic–nematic.*
- ○ *Nematic–isotropic.*
- ■ *Smectic–isotropic.*
- ⊕ *Smectic I–smectic II.*

nematic–isotropic transition point curves which invariably fall along their entire length. Moreover, the curve for the nitro-compounds is very similar to that for the purely smectic alkyl esters of 4-*n*-alkoxy-4′-carboxydiphenyls (Gray, Hartley, and Brynmor Jones, unpublished work), whose smectic–isotropic transitions follow a curve which rises and then falls. This is, of course, the normal curve for smectic–nematic and smectic–isotropic transition points in a homologous series, and it shows that the relative stability of a smectic phase to the isotropic liquid in a purely smectic series is the same as the relative stability of a smectic phase to the nematic phase and to the isotropic liquid in a series exhibiting both phase types. In Fig. 4 the curve through the smectic II–isotropic transitions is drawn to pass above the optimum point for the nonyl ether. This is because there is known to be an odd–even alternation for smectic–isotropic transitions in the esters of 4-*n*-alkoxy-4′-carboxydiphenyls, and consequently the curve through the nitro-decyl, -dodecyl, -hexadecyl, and -octadecyl ethers should pass above the point for the nonyl ether. No comment can be made about the smectic II–smectic I transitions which could not be determined.

The absence of nematic properties in these compounds can be related to the high dipole moment of the nitro-group (4·24 μ), which operates at about 60° to the molecule's long axis, which, in the dimer, will be parallel to the 3 : 4-bond. Now, mesomorphic esters, *e.g.*, 4-*n*-alkoxy-4′-carboxydiphenyl alkyl esters, are always purely smectic and they, too, have a dipole acting across the molecule at about 70° to the long axis :



(4·24 μ)



(*ca.* 1·9 μ)

Thus, the nitro-compounds have the same characteristics as other typically smectic compounds, and the dipole will tend to align the molecules in parallel layers so that the dipoles reinforce one another.

A brief preliminary account of the effect of substitution on the mesomorphism of the 6-alkoxy-2-naphthoic acids has already been given (Gray and Brynmor Jones, *Nature*, 1952, **170**, 451). At that time it was thought that the mesophases in the 5-nitro-compounds consisted of a smectic and a nematic phase, and that the phases were short but enantiotropic. A detailed microscopic examination and rigid purification of the materials have shown this to be wrong, and the compounds are now known to show monotropic phases. Moreover, the use of the microscope heating block (Gray, *Nature*, 1953, **172**, 1137) has resulted in more accurate determination of the transition points, with the result that there are slight differences between the phase lengths now recorded and those originally reported.

Because of their similarity, it is possible to compare the three series of 5-halogeno-acids with the unsubstituted 6-alkoxy-2-naphthoic acids. In all four series, the meso-

TABLE 1

5-Substituent	H	Cl	Br	I
Average transition of mesophase to isotropic liquid (C_6—C_{18})	181·9°	193·6°	190·4°	180·9°
Change in transition temperature from unsubstituted	—	+11·7°	+8·5°	−1°
Increase in breadth from unsubstituted (Å)	—	0	0·22	0·6
Change in dipole moment from unsubstituted (μ)	—	1·73	1·71	1·48

morphic–isotropic transitions can be determined accurately for the pentyl to octadecyl ethers, and from these an average mesomorphic–isotropic transition temperature has been obtained for each series. The results show that there is an increase in average stability of the mesophase from the unsubstituted to the 5-chloro- and 5-bromo-acids, and a slight decrease from unsubstituted to the 5-iodo-acid. These results are summarised in Table 1.

As the size of the halogen substituent increases, there is a gradual decrease in mesomorphic stability in the 5-halogeno-series—which is in agreement with the behaviour of the 4-alkoxy-3-fluoro- and -3-chloro-benzoic acids (Gray and Brynmor Jones, *J.*, 1954, 2556). However, in the 4-alkoxybenzoic acids there is also a substantial decrease in stability on substitution in the 3-position, whereas the unsubstituted naphthoic acids are less stable in their phases than the 5-chloro- and 5-bromo-derivatives, and only a little more stable than the 5-iodo-acids. These differences arise from the smaller increase in breadth which any one substituent produces in the 5-position in a naphthoic acid compared with in the 3-position in a benzoic acid. In the naphthoic acids the substituent is in part accommodated in the space between the 5-carbon atom and the line determining the perimeter of the molecule, as shown in the inset. This space is large enough to accommodate a chlorine atom, so that the calculated breadths (*d*) for the unsubstituted and the 6-alkoxy-5-chloro-2-naphthoic acids are the same, whereas a 4-alkoxy-3-chlorobenzoic acid is broader by 0·75 Å than a 4-alkoxybenzoic acid. Since the changes in breadth are less in the naphthoic acids, the mesomorphic stability would not be expected to decrease to the same extent as in the benzoic acids. The greater stability of the 5-chloronaphthoic acids must therefore arise from the introduction of the C–Cl dipole, which, in these compounds, is not counteracted by a breadth increase as in the 4-alkoxy-3-chlorobenzoic acids. The increase in intermolecular cohesion which accompanies this dipole (1·73 μ) is equal to 11·7° (Table 1). From unsubstituted to 5-bromo-acid, the relative mesomorphic stability increase is less (8·5°), and this may be attributed to the slightly smaller C–Br dipole moment and to the increase in breadth of 0·22 Å occasioned by the larger bromine atom—both of these effects will reduce the intermolecular cohesion and the thermal stability of the bromo-acids. The 5-iodo-acids show a relative stability *decrease* of 1·0° compared with the unsubstituted naphthoic acids, and, again, this may be related to the smaller C–I dipole and to the fact that the large iodine atom increases the molecular breadth by 0·6 Å. However, it cannot yet be stated with any certainty whether or not the effect of a substituent on a compound's mesomorphic behaviour is directly related to its size and to the dipole it produces.

The average smectic–nematic transition temperatures for the nonyl, decyl, and dodecyl ethers of the four series have also been considered, and the results are summarised in Table 2.

TABLE 2.

5-Substituent	H	Cl	Br	I
Average smectic–nematic transition temp. (C_9–C_{12}) ...	148·5°	185·8°	181·5°	163·7°

Here again there is a decrease in the thermal stability as the size of the substituent increases, but, in all cases, the stability is greater than in the unsubstituted acid. The dipole moment would seem here to have a greater effect in determining the temperature at which the smectic phase becomes nematic, than it has on the transition of the nematic to the isotropic liquid. The effect of a dipole acting across a molecule in increasing the thermal stability of the smectic phase has already been discussed under the 5-nitro-compounds.

In order to compare the behaviour of the 5-nitro-derivatives with the other series, the average smectic–nematic and smectic–isotropic transition temperatures for the decyl to octadecyl ethers of the 5-halogeno- and the unsubstituted acids must be related to the average smectic II–isotropic transition temperature for the same range of 5-nitro-compounds. These figures are summarised in Table 3.

TABLE 3.

5-Substituent	H	Cl	Br	I	NO_2
Average smectic–nematic or smectic–isotropic transition temp. (C_{10}–C_{18})	156·25°	181·25°	176·9°	165·4°	163°

The behaviour of the chloro-, bromo-, and iodo-acids relative to the unsubstituted naphthoic acids is similar to that shown in Table 2, but an indication of the difficulty in

relating the size and dipole of a substituent to its effect on mesomorphic behaviour is given by the low average transition temperature of the 5-nitro-series. The C–NO_2 dipole (4·24 μ) might have been expected to increase the relative thermal stability to a considerable extent, particularly as the increase in breadth due to the nitro-group is only 0·48 Å, considerably less than that arising from an iodine atom. If a substituent's dipole is indeed directly related to the substituent's effect on mesomorphic stability, some other factor must be reducing the intermolecular cohesion which should arise from the nitro-group's dipole moment. Molecular models indicate that the nitro-group, as a result of rotation about the C–N bond, is forced out of the plane of the naphthalene ring through the steric effect of the hydrogen atom on the 8-carbon atom. The result is a thickening of the molecule which would reduce the intermolecular cohesion between the planes of neighbouring molecules. It is difficult to estimate the extent of this effect, or to decide whether it is sufficient to account for the low average thermal stability of the nitro-compounds. A study of the behaviour of an analogous type of molecule, a mesomorphic, nitro-substituted, alkoxyarene-carboxylic acid, in which the nitro-group can remain planar, would be of interest, and this is now being made.

Experimental

(M. p.s are corrected for exposed stem.)

Determination of Transition Temperatures.—These temperatures (solid–solid, solid–smectic and nematic, smectic–nematic, and smectic and nematic–isotropic) were determined in an electrically heated microscope block (Gray, *Nature*, *loc. cit.*). The procedure adopted for the observation of the monotropic changes was the same as described for the 4-alkoxy-3-halogenobenzoic acids (Gray and Brynmor Jones, *J.*, 1954, 2556). All transitions between mesophases, and those from the isotropic liquid to the mesophase, were reversible at the same temperature. The nematic phases of the 5-halogeno-derivatives appeared from the isotropic liquid as spherical droplets which coalesced to give, in general, homogeneous plane structures containing varying numbers of threads. In the hexadecyl and octadecyl ethers, the formation of the smectic phase from the isotropic liquid became apparent by the appearance of bâtonnets which, in all cases, yielded fine mosaics comprised of tiny focal-conic groups. In the nitro-series, smectic phase I was also of this type, but smectic II was almost totally homœotropic, except for minute patches of focal-conic groups formed by the coalescing bâtonnets. These, although very transient, were much larger than those observed in the purely smectic 5-halogeno-derivatives.

Polymorphism became increasingly marked as the size of the halogen substituent increased. It was also pronounced in the 5-nitro-series. The data for the enantiotropic polymorphic transitions are summarised below, where solid I is the stable solid at room temperature.

Alkyl	Solid I–solid II transition temp.
6-n-Alkoxy-5-chloro-2-naphthoic acids	
Pentyl	162°
Hexyl	134
The butyl, octyl, and nonyl ethers exhibit a monotropic solid.	
6-n-Alkoxy-5-iodo-2-naphthoic acids	
Propyl	213°
Butyl	203
Pentyl	176·5
Hexyl	162
Heptyl	149·5
Octyl	138
Nonyl	125
Decyl	119
Dodecyl	113
Hexadecyl	103
Octadecyl	118

Alkyl	Solid I–solid II transition temp.
6-n-Alkoxy-5-bromo-2-naphthoic acids	
Pentyl	163°
Hexyl	163
Heptyl	144·5
Octyl	122
The butyl ether exhibits a monotropic solid.	
6-n-Alkoxy-5-nitro-2-naphthoic acids	
Octyl	153·5°
Nonyl	112
Decyl	133
Dodecyl	131
Hexadecyl	107
Octadecyl	75·5
The pentyl ether exhibits a monotropic solid.	

Preparation of Materials.—The 6-alkoxy-5-chloro-2-naphthoic acids were prepared by alkylation of 5-chloro-6-hydroxy-2-naphthoic acid prepared from 6-methoxy-2-naphthoic acid (Gray and Brynmor Jones, *J.*, 1954, 678). Alkylation of 5-bromo-6-hydroxy-2-naphthoic acid

invariably left some unalkylated material, and, since this is difficult to remove, all the 6-alkoxy--5-bromo-, -5-iodo-, and -5-nitro-2-naphthoic acids were prepared by bromination, iodination, and nitration of the pure 6-alkoxy-2-naphthoic acids (*idem*, *loc. cit.*).

5-Chloro-6-methoxy-2-naphthoic Acid.—6-Methoxy-2-naphthoic acid (5·05 g., 1 mol.) and dichloramine-T (3 g., 0·5 mol.) were dissolved separately in glacial acetic acid (150 ml. and 20 ml., respectively) at 40°. The solutions were mixed, a few drops of concentrated hydrochloric acid were added, and the mixture was heated for 1 hr. on the water-bath. Cooling yielded the colourless *chloro-acid* (4·75 g., 82%), and the toluene-*p*-sulphonamide remained in solution. The acid was filtered off, washed with glacial acetic acid, and crystallised from the same solvent. The yield of colourless needles was 80%, m. p. 320·5° (Found: C, 60·7; H, 3·9; Cl, 15·2. $C_{12}H_9O_3Cl$ requires C, 60·9; H, 3·8; Cl, 15·0%).

5-Chloro-6-hydroxy-2-naphthoic Acid.—The methyl ether (23·7 g.) was suspended in a solution of 48% hydrobromic acid (250 ml.) in glacial acetic acid (250 ml.). The mixture, after being refluxed until a solution was obtained (14—16 hr.), was poured into water (1 l.), and the pale pink precipitate (20 g.; m. p. 270—275°) was filtered off, washed with water, and dried. Soxhlet extraction with ether removed some insoluble, high-melting material, and the ether solution yielded *5-chloro-6-hydroxy-2-naphthoic acid* (18·5 g., 83%), m. p. 271° (decomp.). Crystallisation from a small volume of absolute methyl alcohol, followed by sublimation at 160—180°/1—2 mm., yielded colourless needles, 17·6 g. (79%), m. p. 279° (decomp.) (Found: C, 59·1; H, 3·3; Cl, 16·0. $C_{11}H_7O_3Cl$ requires C, 59·4; H, 3·15; Cl, 15·9%).

6-Alkoxy-5-chloro-2-naphthoic Acids.—5-Chloro-6-hydroxy-2-naphthoic acid (2·23 g., 1 mol.), potassium hydroxide (1·1 g., 2 mols.), water (5 ml.), ethyl alcohol (40 ml.), and the *n*-alkyl halide (1·2 mols.) were refluxed for 8 hr. (alkyl iodides) or 16 hr. (alkyl bromides). Aqueous potassium hydroxide (10 ml., 10%) was added, and the refluxing continued for 2 hr. to hydrolyse any ester. The acids were obtained as pure, colourless products after two crystallisations from glacial acetic acid and one from 95% ethyl alcohol, and, in the case of the hexyl—decyl, dodecyl, hexadecyl, and octadecyl ethers, one sublimation at 1—2 mm. The yields after the first crystallisation were 80—90%.

6-n-*Alkoxy-5-chloro-2-naphthoic acids.*

Alkyl	Found (%) C	H	Cl	Formula	Required (%) C	H	Cl
Ethyl	62·3	4·4	14·3	$C_{13}H_{11}O_3Cl$	62·3	4·4	14·2
Propyl	63·5	5·0	13·5	$C_{14}H_{13}O_3Cl$	63·5	4·9	13·4
Butyl	64·8	5·5	12·8	$C_{15}H_{15}O_3Cl$	64·6	5·4	12·75
Pentyl	65·8	5·8	12·1	$C_{16}H_{17}O_3Cl$	65·6	5·8	12·1
Hexyl	66·6	6·2	11·4	$C_{17}H_{19}O_3Cl$	66·6	6·2	11·6
Heptyl	67·4	6·6	11·1	$C_{18}H_{21}O_3Cl$	67·4	6·55	11·1
Octyl	68·6	6·9	10·6	$C_{19}H_{23}O_3Cl$	68·2	6·9	10·6
Nonyl	68·9	7·2	10·1	$C_{20}H_{25}O_3Cl$	68·9	7·2	10·2
Decyl	69·5	7·5	9·8	$C_{21}H_{27}O_3Cl$	69·5	7·45	9·8
Dodecyl	70·7	8·0	9·1	$C_{23}H_{31}O_3Cl$	70·7	7·9	9·1
Hexadecyl	72·4	8·9	7·7	$C_{27}H_{39}O_3Cl$	72·6	8·7	7·95
Octadecyl	73·4	9·1	7·4	$C_{29}H_{43}O_3Cl$	73·3	9·1	7·5

6-n-*Alkoxy-5-bromo-2-naphthoic acids.*

Alkyl	Found (%) C	H	Br	Formula	Required (%) C	H	Br
Methyl	51·1	3·1	28·5	$C_{12}H_9O_3Br$	51·25	3·2	28·5
Ethyl	52·8	3·8	26·9	$C_{13}H_{11}O_3Br$	52·9	3·7	27·1
Propyl	54·2	4·1	25·9	$C_{14}H_{13}O_3Br$	54·4	4·2	25·9
Butyl	55·5	4·6	24·8	$C_{15}H_{15}O_3Br$	55·7	4·6	24·8
Pentyl	57·2	4·9	23·6	$C_{16}H_{17}O_3Br$	57·0	5·0	23·7
Hexyl	58·1	5·3	22·7	$C_{17}H_{19}O_3Br$	58·1	5·4	22·8
Heptyl	59·3	5·8	21·7	$C_{18}H_{21}O_3Br$	59·2	5·75	21·9
Octyl	60·3	6·0	20·9	$C_{19}H_{23}O_3Br$	60·2	6·1	21·1
Nonyl	61·0	6·3	20·5	$C_{20}H_{25}O_3Br$	61·1	6·4	20·4
Decyl	61·9	6·6	19·4	$C_{21}H_{27}O_3Br$	61·9	6·6	19·7
Dodecyl	63·4	7·0	18·4	$C_{23}H_{31}O_3Br$	63·4	7·1	18·4
Hexadecyl	66·1	7·9	16·2	$C_{27}H_{39}O_3Br$	66·0	7·9	16·3
Octadecyl	67·1	8·3	15·4	$C_{29}H_{43}O_3Br$	67·0	8·3	15·4

6-Alkoxy-5-bromo-2-naphthoic Acids.—The 6-alkoxy-2-naphthoic acid (1 mol.), dissolved in the minimum volume of glacial acetic acid at 80°, was treated with bromine (1 mol.) in twice its volume of glacial acetic acid. The mixture was stirred at 80° for 20 min., although part of the product had separated from solution almost as soon as all the bromine had been added. When the reaction mixture had cooled, an almost quantitative yield of the nearly pure 5-bromo-acid was obtained. In each case two crystallisations from glacial acetic acid yielded the pure acids.

6-Alkoxy-5-iodo-2-naphthoic Acids.—A solution of iodine monochloride was prepared by dissolving sodium iodide (0·1 mol.) in boiling glacial acetic acid (50 ml.) and adding this carefully, with stirring and cooling, to a solution of dichloramine-T (0·05 mol.) in warm glacial acetic acid (25 ml.). To the solution of the 6-alkoxy-2-naphthoic acid (0·1 mol.), dissolved in the minimum volume of glacial acetic acid at 80°, the solution of iodine monochloride (0·1 mol.) was added rapidly with stirring. Almost immediately, the iodo-acid began to crystallise, but the mixture was kept at 80° for 20 min. to ensure complete iodination. Two crystallisations from glacial acetic acid gave the iodo-acids in 85—90% yields. Further crystallisation from this solvent did not raise the m. p.

6-n-*Alkoxy-5-iodo-2-naphthoic acids.*

	Found (%)				Required (%)		
Alkyl	C	H	I	Formula	C	H	I
Methyl	44·0	2·7	38·5	$C_{12}H_9O_3I$	43·9	2·7	38·7
Ethyl	45·7	3·3	37·4	$C_{13}H_{11}O_3I$	45·6	3·2	37·1
Propyl	47·4	3·8	35·5	$C_{14}H_{13}O_3I$	47·2	3·65	35·7
Butyl	48·6	4·1	34·4	$C_{15}H_{15}O_3I$	48·7	4·1	34·3
Pentyl	50·1	4·4	32·9	$C_{16}H_{17}O_3I$	50·0	4·4	33·1
Hexyl	51·4	4·7	31·8	$C_{17}H_{19}O_3I$	51·25	4·8	31·9
Heptyl	52·5	5·0	30·6	$C_{18}H_{21}O_3I$	52·4	5·1	30·8
Octyl	53·6	5·3	30·0	$C_{19}H_{23}O_3I$	53·5	5·4	29·8
Nonyl	54·4	5·8	28·8	$C_{20}H_{25}O_3I$	54·6	5·7	28·9
Decyl	55·5	5·9	27·7	$C_{21}H_{27}O_3I$	55·5	5·95	27·9
Dodecyl	57·4	6·5	26·6	$C_{23}H_{31}O_3I$	57·3	6·4	26·35
Hexadecyl	60·2	7·4	24·0	$C_{27}H_{39}O_3I$	60·2	7·25	23·8
Octadecyl	61·5	7·7	22·6	$C_{29}H_{43}O_3I$	61·5	7·6	22·4

6-Alkoxy-5-nitro-2-naphthoic Acids.—To the 6-alkoxy-2-naphthoic acid (1 g.), dissolved in the minimum volume of glacial acetic acid at 55—60° (the hexadecyl and octadecyl ethers were used as a suspension in 50 ml. of the solvent), a solution of fuming nitric acid (4 ml.) in glacial acetic acid (4 ml.) was added with stirring. The temperature was raised to 75—80°, and kept there for 10 min., clear solutions then being obtained in all cases. When cold, the pale yellow, crystalline 5-nitro-derivatives were separated and, after being washed with glacial acetic acid and water, they were dried. The yields of crude material were 85—95%, but constant m. p.s were only attained after several crystallisations from glacial actic acid (once), 95% ethyl alcohol (twice), toluene (once), and 95% ethyl alcohol, in this order.

6-n-*Alkoxy-5-nitro-2-naphthoic acids.*

	Found (%)				Required (%)		
Alkyl	C	H	N	Formula	C	H	N
Methyl	58·2	3·6	5·6	$C_{13}H_9O_5N$	58·3	3·6	5·7
Pentyl	63·4	5·7	4·8	$C_{16}H_{17}O_5N$	63·4	5·6	4·6
Octyl	66·2	6·8	4·1	$C_{19}H_{23}O_5N$	66·1	6·7	4·1
Nonyl	67·0	6·9	3·9	$C_{20}H_{25}O_5N$	66·85	7·0	3·9
Decyl	67·5	7·2	3·8	$C_{21}H_{27}O_5N$	67·6	7·2	3·75
Dodecyl	68·5	7·7	3·5	$C_{23}H_{31}O_5N$	68·8	7·7	3·5
Hexadecyl	71·1	8·6	3·05	$C_{27}H_{39}O_5N$	70·9	8·5	3·1
Octadecyl	71·9	8·9	2·85	$C_{29}H_{43}O_5N$	71·75	8·9	2·9

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THE UNIVERSITY OF HULL. [*Received, August 9th,* 1954.]

The Extraction and Purification of Scandium.

By R. C. Vickery.

[Reprint Order No. 5725.]

The extraction of scandium from wolframite residues and thortveitite is described. Final purification is effected by ion-exchange techniques which are approached by phase-distribution and acid–base-titration data. Hydrazine-*NN'*-diacetate solutions rapidly remove scandium from mixtures with the rare earths and thorium, and the separation thus achieved is superior to that with citrate or ethylenediamine-*NNN'N'*-tetra-acetate solutions.

The extraction of scandium from its natural sources is hindered by the dearth of knowledge of scandium compounds and their reactions. Because of this lack there is little doubt that techniques used by early workers for the extraction and purification of scandium gave low recoveries of this relatively rare element.

Operations commonly recommended in the treatment of scandium-containing materials involve precipitation of the oxalate or hydroxide. The inefficiency of these procedures and the complications arising from their use are demonstrated in the two following papers.

The scandium employed in these studies was extracted from wolframite residues and thortveitite, being finally purified by ion-exchange techniques. This first paper records these initial operations.

Preliminary Extractions.—Meyer (*Z. anorg. Chem.*, 1907, **60**, 134) and Sterba-Bohm (*Z. Elektrochem.*, 1914, **20**, 289) surveyed the extraction of scandium from ores, but, by use of radioactive scandium and monitoring the progress of extractions by the usual techniques (Vickery, unpublished work), several of the procedures recommended by the earlier workers have been found neither as complete nor as efficient as was once considered.

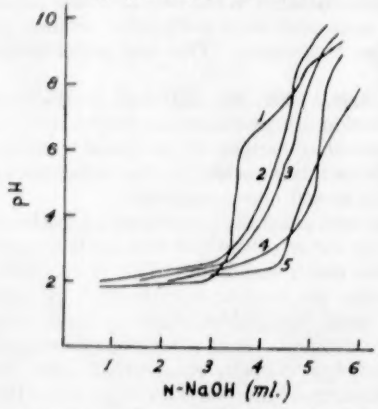
Conventional methods of decomposing siliceous ores generally involve attack by hydrochloric, sulphuric, or hydrofluoric acid. Attack by either of the first two acids generally yields a gelatinous residue of silica which occludes much scandium. This is avoided by using hydrofluoric acid, and the resulting fluorides are readily metathesised by alkali. However, as indicated in the following paper, alkali hydroxides effect at least partial dissolution of scandium and their use is preferably avoided. Acid attack on siliceous ores is generally an untidy procedure however, and Iya (*Compt. rend.*, 1953, **236**, 608) decomposed thortveitite by roasting the finely comminuted mineral with charcoal at 1800° to form carbides which were readily decomposed by dilute hydrochloric acid. Hartley and Wylie (*J. Soc. Chem. Ind.*, 1950, **69**, 1) and Hartley (*J. Appl. Chem.*, 1952, **2**, 24) recently prepared lanthanon chlorides from monazite by chlorination at 700—900° in the presence of carbon, and the possible application of a similar process to thortveitite possessed several attractive features. Scandium chloride sublimes at *ca.* 970° (Klemm *et al.*, *Z. anorg. Chem.*, 1923, **131**, 22 *et seq.*; Fischer *et al.*, *ibid.*, 1939, **242**, 161), and chlorination of thortveitite might well provide a rapid means of decomposing the ore and simultaneously concentrating the scandium by volatilisation. In the present work, however, it was sufficient to provide for the decomposition of thortveitite with the production of scandium in a soluble form. Details of the procedure adopted are given in the Experimental section; insufficient thortveitite was available for determination of the optimum conditions, and the attractive results obtained must be considered as fortuitous rather than designed.

After the commercial extraction of tungsten from some wolframites, the ferruginous residues may contain as much as 0·3% of Sc_2O_3 and it was from residues of this type that Meyer (*loc. cit.*) extracted the scandium on which was based his subsequent work on the element. Such wolframite residues are usually readily soluble in hydrochloric acid, but the presence of much iron in the resulting solution hinders recovery of the scandium. Precipitation of scandium oxalate from such solutions should never be attempted; it is never quantitative and, with iron, vanadium, manganese, and, possibly, uranium present, soluble oxalato-complexes are formed which further inhibit the precipitation of scandium. From such solutions, scandium is best precipitated as silicofluoride or by hydrofluoric acid

after the addition, if necessary, of calcium or lanthanon salts to act as "carriers." Precipitated from hot solutions, the fluorides of the carrier and scandium settle well and are easily filtered or centrifuged off. The wet fluorides are readily decomposed with a minimum of concentrated sulphuric acid, and the sulphates thus obtained are ignited and the residues redissolved in hydrochloric acid for further purification.

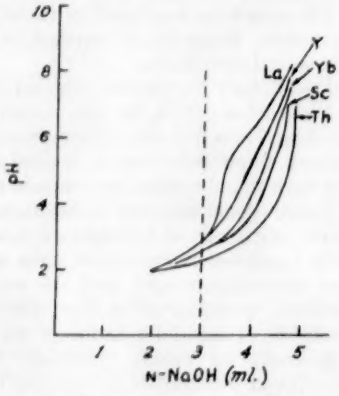
Preliminary Concentration.—Not infrequently, the chloride solutions obtained by the foregoing methods contain varying quantities of, *e.g.*, magnesium, aluminium, iron, calcium, barium, manganese, etc. The individual proportions of these elements may not be high, but the aggregate amount may be sufficient to affect adversely further operations unless their amounts are appreciably diminished. For this purpose precipitation of scandium as double tartrate is as effective as any other method and, although the procedure adopted here was not precisely that of Fischer *et al.* (*Z. analyt. Chem.*, 1951, **133**, 57) it gives excellent yields of scandium when the element is present in concentrations of >3 mg./ml. The double tartrate is readily decomposed by acids, so that a concentrated solution of scandium of *ca.* 80—90% purity was readily obtained.

FIG. 1. *Titration of scandium in polycarboxylate systems.*



1, Imda. 2, Trilo. 3, Enta. 4, Citrate. 5, Hyda. 2×10^{-4}M-Sc. 10^{-3}M-Acid.

FIG. 2. *Titration of rare earths and thorium in citrate systems.*



10^{-4}M-Rare earth. 10^{-3}M-Citrate.

Purification by Ion-exchange.—Because of the known geogenetic association of scandium with the lanthanons, yttrium, and thorium, and the great similarities in the chemistry of these elements, it is inevitable that the final purification of scandium should be more closely concerned with systems containing these elements. Ion-exchange techniques would appear admirably suited for the treatment of such scandium-containing mixtures, but this application has been studied only by Radhakrishnar (*Analyt. Chim. Acta*, **1953**, **8**, 140), Iya (*loc. cit.*), and Iya and Loriers (*Compt. rend.*, 1953, **237**, 1413).

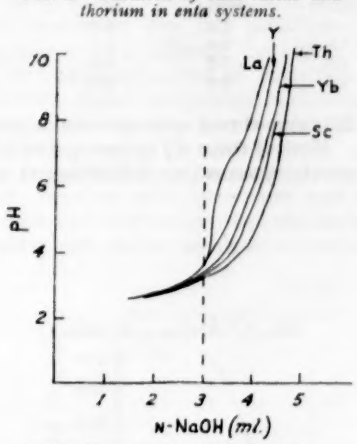
Recent tendencies in ion-exchange studies are towards the use of eluants containing complex-forming anions other than citrate. Hydrazine-*NN'*-diacetic (hyda), nitrilotriacetic (trilo), and ethylenediamine-*NNN'N'*-tetra-acetic (enta) acid have been effectively employed in the ion-exchange separation of the lanthanons (Higgins and Baldwin, ORNL, 1951, 894; Fitch and Russell, *Canad. J. Chem.*, 1951, **29**, 363; *Analyt. Chem.*, 1951, **23**, 1469; Vickery *J.*, 1952, 4357; 1954, 1181; Spedding *et al.*, *J. Amer. Chem. Soc.*, 1954, **76**, 612, 2557), and their use has now been examined in the separation and purification of scandium from thorium and the lanthanons.

Titration and Distribution Studies.—pH titrations of systems containing metal and complex-forming anions yield information of much application to ion-exchange separations. Titration curves are given in Fig. 1 for scandium solutions containing the acids citric,

iminodiacetic (imda), hyda, trilo, and enta. Similar curves are given in Figs. 2 and 3 for systems of thorium, lanthanum, yttrium, ytterbium, and scandium with citric and enta acid.

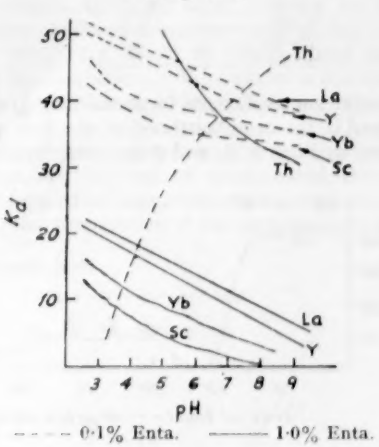
Qualitatively, the titration curves show that complex stability increases in the order La < Y < Yb < Sc < Th for the systems studied. Although stability constants for the

FIG. 3. *Titration of rare earths and thorium in enta systems.*



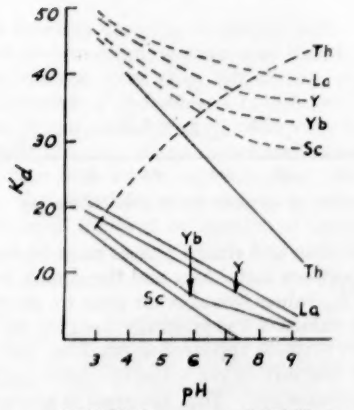
10^{-4}M-Rare earth. 10^{-3}M-Citrate.

FIG. 4. *Distribution coefficients (K_d) for enta systems.*



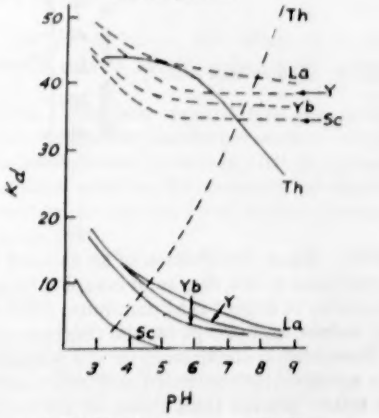
– – – – 0·1% Enta. ——— 1·0% Enta.

FIG. 5. *Distribution coefficients (K_d) for hyda systems.*



– – – – 0·1% Hyda. ——— 1·0% Hyda.

FIG. 6. *Distribution coefficients (K_d) for citrate systems.*



– – – – 0·1% Citrate. ——— 1·0% Citrate.

complexes formed can be derived from the titration data, these are often less significant than the pH values at which the titration curves show greatest divergence from each other. These values of greatest divergence (symbolised here as ∂pH) represent the loci of greatest stability of the complexes formed, and hence are those at which ion exchange should be most selective in the systems studied. ∂pH values obtained are given in the Table. The narrow range between maximum and minimum values for each acid system shows the complexes formed by the metal ions and any one acid to be derived from similar anionic species. With the tervalent ions studied therefore, any variation in behaviour of the

complexes formed must be attributed to variations in stability of the complexes and not to the formation of different anionic species. Variation of ionic species in solution is of great influence in ion-exchange studies but this point of variance does not here appear to arise, so that observations on phase distribution should yield very pertinent data.

Differential pH *values* (∂pH).

System	Citrate	Hyda	Enta
La–Y	5·3	7·5	6·5
Y–Yb	3·9	6·8	4·1
Yb–Sc	4·5	7·3	5·6
Sc–Th	4·5	6·9	5·3

Distribution coefficients for metal ions–Zeokarb 225 resin–eluant systems were determined at, and in the neighbourhood of, the ∂pH values. Plots of these K_d values against pH are shown in Figs. 4, 5, and 6 for enta, hyda, and citrate systems (for definitition of K_d see

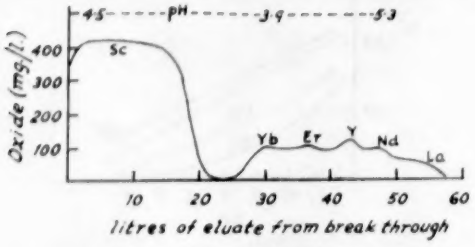


FIG. 7. *Elution with citrate.*

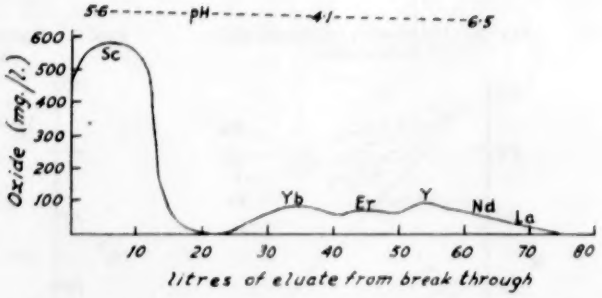


FIG. 8. *Elution with enta.*

p. 250). Since distribution of an element between resin and eluant phases must be largely proportional to the degree of complex formation between metal ions and the eluant, it was reasonable to expect that maximum differences in K_d values would occur close to, or at, the ∂pH values, and except for the thorium–scandium values it was generally found to be so.

Distribution coefficients for the scandium–hyda systems appeared anomalous, but they were consistently confirmed and indicated that the stability of the scandium–hyda complex was much greater than those of the lanthanon complexes. This apparently anomalous behaviour of the scandium–hyda system has now been successfully exploited (see below).

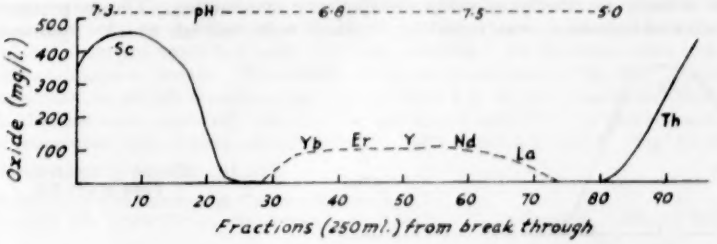
Individual divergencies of K_d values in hyda and enta systems increased with the concentration of acid. In citrate systems this was reversed, so elution should be with 0·1% citrate or 1·0% amino-acid. Since however the sequential position of thorium at the lower eluant concentrations was the reverse of that at the higher, the latter were employed throughout at the possible sacrifice of a certain separational efficiency.

Resin Column Separations.—The influence upon resin-column operations of factors such as eluant flow rate, resin particle size, temperature, etc., have been fully studied by Spedding *et al.* (*J. Amer. Chem. Soc.*, 1947, **69**, 2769 *et seq.*) and require no further consideration here. If solely a result of simple metal-ion size and charge, the sequence of elution of

a thorium–rare earth system from a resin column should be Sc, Yb, Y, La, Th. This has been confirmed now and in the work of Iya and Loriers (*loc. cit.*). Figs. 7, 8, and 9 illustrate the separations achieved with citrate, enta, and hyda eluants respectively. Eluant acidities were adjusted throughout the runs to the ∂pH values appropriate to the elements breaking through from the column. Flow rates of citrate and hyda eluants were chosen somewhat arbitrarily but, as previous (unpublished) work had shown high flow rates to be advantageous with enta eluants, separations with this reagent were conducted at the maximum flow rate possible. Enta eluants again appeared superior to those containing citrate, although the higher flow rates rendered the elution curves less steep. The anomalous behaviour of scandium–hyda complexes shown in titration and phase-distribution data is emphasised in elutions with hyda solutions. Whereas with this eluant no exceptional separations were obtained within the lanthanon series scandium was readily and cleanly removed from the system.

In large-scale work on lanthanon systems containing scandium the latter tends to collect, together with ytterbium and thorium, at the tail of fractionated systems. Scandium and thorium are then eliminated from the ytterbium either during separation of the latter with sodium amalgam or during the prior preparation of the acetates, scandium

FIG. 9. *Elution with hyda.*



and thorium forming insoluble basic salts. The ion-exchange separation of a simple thorium–scandium system was therefore examined. It is accomplished very easily by using citrate, hyda (Fig. 10), or enta eluants.

Recovery of Scandium.—Insufficient was known about how quantitative was precipitation of scandium by alkali hydroxide, fluoride, phosphate, etc., in the presence of complex-forming anions. Unpublished radiochemical studies indicated, however, that precipitation by these ions was rarely complete, so the procedure adopted for recovery of scandium from the eluted fractions simply involved evaporation to dryness twice in the presence of nitric acid, followed by ignition of the residue at *ca.* 900°.

EXPERIMENTAL

Norwegian thortveitite (200 g.) was obtained in small hand-picked lumps. After being ground to 200 mesh, a portion gave analyses Ln_2O_3 12·1% and Sc_2O_3 33·8%, *i.e.*, close to the most recent results for Norwegian thortveitite by Marble and Glass (*Amer. Mineral.*, 1942, **27**, 696). The wolframite residues (4 kg. available) were of unknown, but possible Nigerian, origin and had been found to contain 0·08% of Sc_2O_3.

The individual lanthanons employed had been derived from various sources during past years and had been purified by various methods to >99% purity. The thorium was of B.D.H. laboratory reagent grade, and the scandium employed for the titration and distribution studies was "Specpure." Other general chemicals were of "AnalaR" grade. Enta acid was the "Sequestrene" material supplied by the Geigy Co. Trilo acid was kindly supplied by Dr. J. K. Marsh. Hyda acid was prepared and purified as recorded by Vickery (*J.*, 1954, 385). Imda acid was prepared from hyda acid by Bailey and Read's method (*J. Amer. Chem. Soc.*, 1914, **36**, 1747).

pH titrations were followed through a glass–calomel electrode system on a Cambridge electrometer. Distribution coefficients were determined by equilibrating the exchange resin

(Zeo-Karb 225; Permutit Co.) with the appropriate solutions during 24—48 hr. with continuous shaking, then evaporating the mother-liquors to dryness, and igniting and weighing the residue. The resin was also ignited and the ash weighed for check data. K_d values were then obtained from the equation $K_d = (M_s/M_L)(V/M)$, where M_s and M_L are fractions of the cation in the resin and liquid phases respectively, V = volume of solution, and M = mass of resin.

Chlorination of Thortveitite.—The simple furnace employed for chlorination was arranged horizontally and rotated on its axis. A Vitreosil tube (18" × 1¼") was fitted with internal baffles of ¼"-diam. silica rod fused to the main tube 1" from each end. The tube was mounted inside a platinum-wound tube-furnace, with inlet and outlet tubes for chlorine provided by silica tubing penetrating rubber bungs at each end of the main tube. The entry tube for chlorine was fitted with a rotating adaptor, and the main tube was rotated at 8 r.p.m. by the friction drive of a rubber band encircling the rubber bung at the entry end and attached to a small, geared-down, electric motor.

The finely comminuted thortveitite was thoroughly mixed with an equal weight of wood charcoal and hand-granulated with the addition of a small volume of 10% dextrin solution. 75-g. quantities of the granules thus obtained were charged into the furnace tube and chlorinated for 4 hr. at 800—850° with 250 ml. of chlorine per hr. Insufficient material was available for a critical survey of factors influencing efficienty but, in the six charges treated, temperature was varied from 800° to 850°, chlorine flow-rate from 150 to 250 ml./min. (*ca.* 0·45—0·75 g./min.), *i.e.*, 2·2—3·3 times the theoretical quantity, and the time of reaction was reduced from 4½ to 3 hr., all without manifestly affecting the quantity of scandium chloride produced. Each charge, after chlorination, was separately leached with 200 ml. of 1% hydrochloric acid,

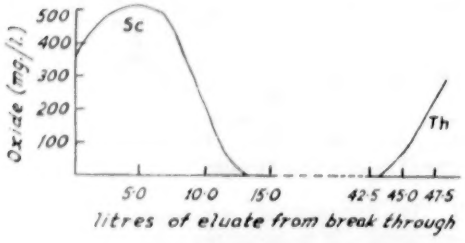


FIG. 10. *Elution of scandium-thorium with hyda at* pH 7·0.

filtered from carbon, silica, etc., evaporated to a syrup, and diluted to 250 ml. 10 ml. of each extract were taken for determination of scandium and lanthanon contents which, with the mild variations introduced in treatment, remained remarkably constant. Each extraction of the equivalent of 37 g. of thortveitite yielded Sc_2O_3 12·3 ± 0·1 g. and Ln_2O_3 4·3 ± 0·1 g., *i.e.*, average recoveries of 98·3 and 95·9% respectively. After analysis the solutions were combined and retained for further treatment.

The wolframite residues were received in a fine state of sub-division and required no further comminution. Treated in 800-g. quantities, these residues were sifted into 2·5 l. of 50% v/v hydrochloric acid at *ca.* 75° with continuous stirring. Digestion was carried out for 90 min., whereafter the slurry was allowed to settle and was then centrifuged. The mother-liquor was first decanted, then filtered off. The extracted solutions were individually evaporated to *ca.* 500 ml., combined, and then further evaporated to *ca.* 1500 ml. Lanthanum chloride (equiv. to 10 g. of La_2O_3) was added to the solution, and sulphur dioxide was passed in to reduce tervalent iron. The pH of the solution was adjusted to 5·2 and concentrated hydrofluoric acid was slowly added with constant stirring until no further precipitate appeared. The pH was then 3·4 and some 35 ml. of acid had been added. After the mixture had been kept overnight the mother-liquor was first decanted, then filtered, from the precipitated fluorides which, after being washed twice by decantation, were digested with boiling 30% sulphuric acid (200 ml.) for 30 min. and the solution was then evaporated. The residue was ignited to oxide at 1000°.

The final weight of mixed oxides was 14·4 g., so that, with allowance for the 10 g. of La_2O_3 added, a recovery of 4·4 g. from the wolframite had been obtained. This is greater than expected from the original analysis, but the final oxide was grossly impure and undoubtedly recovery of scandium had not been complete. An optimistic approximation of scandium recovery would be *ca.* 2·5 g., *i.e.*, 75—80%. The recovered oxides were redissolved in dilute hydrochloric acid, and the solution obtained added to that from the thortveitite.

To the mixed solutions (derived from thortveitite and wolframite) was added tartaric acid (250 g.), the whole was warmed to *ca.* 60°, and precipitation effected by the addition of ammonia solution to increase the pH to *ca.* 7.

The thick slurry was immediately filtered off at the pump and washed with 5% ammonium tartrate solution (1 l.). After drying, the double tartrate was ignited at 900° in varying portions. The final combined oxides (85 g.) were obviously impure, and their solution in hydrochloric acid showed strong spectral absorption lines of the lanthanons when examined with a hand-spectroscope. This chloride solution was then purified by ion-exchange.

Except for the change in resin from Dowex 50 to Zeo-Karb 225, the resin columns used were identical in construction with those previously described (Vickery, *loc. cit.*). Fractions eluted by citrate and hyda were collected at 250 ml./hr., and those eluted by enta at 1 l./hr. Each eluted fraction was evaporated to dryness, and when a mineral residue appeared it was redissolved in hydrochloric acid and held for further examination. The first fractions were treated with ammonium tartrate for detection and determination of scandium. Elution of the lanthanons and yttrium was followed spectrophotometrically as far as possible.

Initial elutions were carried out on 30 ml. of the impure scandium solution containing 5 g. of solids, *i.e.*, *ca.* 3·5 g. of Sc_2O_3. When the efficiency of hyda elution and applicability of the K_d and pH data had been confirmed, three resin columns were allocated for elutions with hyda, and one each retained for comparative citrate and enta elutions. In all cases the aliquot part taken of initial solutions was increased to 60 ml., *i.e.*, 10 g. of solids equiv. to *ca.* 7·0 g. of Sc_2O_3.

For observation of the ease of separating thorium from scandium, the final 20 ml. of the impure scandium solution were mixed with 40 ml. of 20% thorium chloride solution, and the mixture eluted from the resin bed with 1% hyda solution. All fractions were examined for thorium by additions of iodate. The results obtained are shown in Fig. 9. To confirm this ease of separation in simple scandium–thorium systems 5 g. of pure scandium oxide from the final hyda elutions were converted into chloride and mixed with 10 g. of thorium chloride, and the whole was eluted from a resin column with 1% hyda solution at pH 7. Fig. 10 records the results.

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Scandium Hydroxide and Scandate Ions.

By R. C. VICKERY.

[Reprint Order No. 5726.]

The precipitation of scandium hydroxide by alkali, or ammonium, hydroxide solutions is followed turbidimetrically and shown to be incomplete owing to formation of scandate or hexamminoscandium ions according to the alkali hydroxide used. The composition of the scandate is indeterminable; the ammino-complex is considered to be $[Sc(NH_3)_6]^{3+}$. Polarographic studies on the scandate complex give $-1{\cdot}88 \pm 0{\cdot}01$ v for the half-wave potential of the Sc^{3+} ion.

THE addition of hydroxyl ion to solutions of simple scandium salts precipitates white, gelatinous scandium hydroxide. The water solubility of this hydroxide has been stated as *ca.* 5×10^{-7} mole/l. (Moeller and Kremers, *Chem. Reviews*, 1945, **37**, 116) but precipitation is never complete within this limit.

Although Sterba-Bohm and Melitchar (*Coll. Czech. Chem. Comm.*, 1935, **7**, 131) had earlier claimed the isolation of $K[Sc(OH)_5H_2O].3H_2O$ from potassium hydroxide–scandium hydroxide solutions, and Weiser and Milligan (*J. Phys. Chem.*, 1938, **42**, 669, 673) had confirmed the "peptisation" of scandium hydroxide by alkali hydroxide, Fischer and Bock (*Z. anorg. Chem.*, 1942, **249**, 146) considered scandium hydroxide to be only soluble in concentrated alkali hydroxide solutions. Radiochemical studies (unpublished) have, however, confirmed the earlier work.

Precipitation and redissolution of scandium hydroxide are readily followed turbidimetrically (see Fig. 1). Discontinuities at low alkali : scandium ratios may indicate the

formation of basic salts at *ca.* pH 6·5. Turbidity, and thus immediate precipitation, attains its maximum at pH 8·5 with an alkali : scandium ratio of 3—4·1 : 1. Redissolution of the hydroxide commences at an alkali : scandium ratio of 5 : 1.

Ivanov-Emin and Oustromov (*J. Gen. Chem., U.S.S.R.*, 1944, **14**, 772) gave pH 4·8—4·9 for the precipitation incidence of scandium hydroxide and this is largely confirmed by the present work. The Russian workers claimed, however, that precipitation is complete at pH 5·45 after the addition of 1·8 equivs. of sodium hydroxide. It is now thought that the pH curves obtained by them provide additional evidence for the formation of basic compounds, as suggested by the earlier stages of the turbidimetric curves. This belief is enhanced by the Russian workers' indication that, before final coagulation, the precipitate is $Sc(OH)_xA,yH_2O$ where A is the anionic species present and x varies with the valency of A.

The incompleteness even of the maximum precipitation by sodium hydroxide is shown by comparison with the turbidity attained by a slurry of scandium hydroxide equivalent in concentration to the scandium solution titrated.

Replacement of sodium hydroxide by potassium hydroxide does not materially alter the progress of precipitation and redissolution of scandium hydroxide. Precipitation by

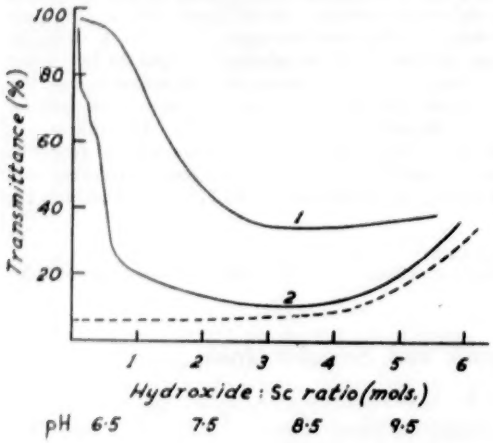


FIG. 1. *Precipitation of scandium hydroxide.* Turbidity produced by (1) aq. NH_3, (2) NaOH, (broken line) pure $Sc(OH)_3$ in the same concentrations.

aqueous ammonia is more complicated, however, and, as shown more fully below, involves the formation, not of an anionic scandate ion, but of a cationic ammino-complex. Whilst results on the precipitation of scandium hydroxide by alkali hydroxide varied insignificantly throughout the experiments, conditions for redissolution of the hydroxide varied appreciably with concentrations of reactants. With increasing scandium concentrations, higher pH and OH : Sc ratios were necessary for redissolution (Fig. 2). The complex ion found in alkaline solution can be decomposed by the judicious addition of acid. Scandium hydroxide is first precipitated and then redissolves as acidity increases below *ca.* pH 4·5. Comparison of turbidity curves approached from the acid and the alkaline side showed only slight hysteresis.

That the complex is anionic is indicated by its behaviour with ion-exchange resins. Cation-exchangers (Dowex-50 and Zeo-Karb 225) showed negligible adsorption of scandium from alkaline solutions, but almost complete extraction was obtained on anion-exchange resins (Amberlite IRA-400 and Deacidite FF). Attempts were made to evaluate the charge on the complex ion by determining the ion displaced from the resin (fluoride), but the results were inexplicably inconsistent (Table 1).

The successful investigation of other complex ions by polarography (Lingane, *Chem. Reviews*, 1941, **29**, 1) prompted the application of this technique to the present study. Leach and Terrey (*Trans. Faraday Soc.*, 1937, **33**, 480) obtained $-1{\cdot}8_4$ v for the half-wave potential of Sc^{3+} in acid solution, but we have been unable to confirm completely their

deposition curves. Particularly was this so when potassium chloride was the supporting electrolyte. The decomposition potential of the potassium ion (−1·9 v) lies so close to the half-wave potential of scandium that separation of the Sc^{3+} and the K^+ wave was not

TABLE 1. *Ion-exchange data for scandate ion.*

Initial solution: 200 ml. at pH 9·7 containing 0·69 g. of Sc_2O_3.

Resin	Sc_2O_3 (g.) in eluate	F (g.) in eluate	Ratio Sc : F	Sc_2O_3 (g.) in eluate	F (g.) in eluate	Ratio Sc : F
Amberlite IRA-400	0·010	0·775	1 : 2·7		Deacidite FF	
" "	0·015	1·085	1 : 3·8	0·012	0·515	1 : 1·8
Dowex-50	0·65	—	—	0·009	0·918	1 : 3·2
Zeo-Karb 225	0·66	—	—	0·019	0·766	1 : 2·7
				0·003	0·667	1 : 2·3

possible (Fig. 3*a*); similar results were obtained with lithium (−2·0 v) and barium (−1·8 v) chlorides as supporting electrolytes. Adequate waves were, however, obtained with tetramethylammonium ions (−2·6 v) as the support, and with this system an $E_{\frac{1}{2}}$ value of

FIG. 2. pH *of scandium hydroxide redissolution.*

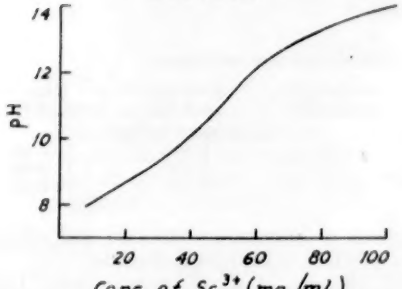
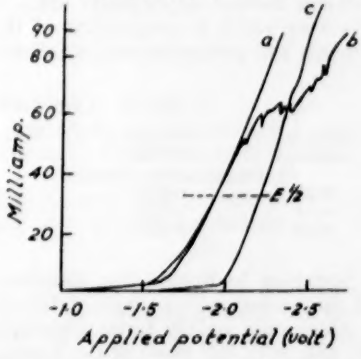


FIG. 3. *Polarography of scandium ions.*



−1·88 ± 0·01 v was obtained for the Sc^{3+} ion (Fig. 3*b*). No evidence was found for the existence of Sc^{2+} ions (cf. Noddack and Brukl, *Angew. Chem.*, 1937, **50**, 362).

The half-wave potential of a simple ion is known to be displaced to more negative values on complex formation. Such behaviour was shown by scandium in alkaline solution (Fig. 3*c*), but the shift in potential obliterated the diffusion-curent plateau between the scandium and tetramethylammonium waves, so that it was impossible to determine the precise position of the displaced scandium wave; a shift of *ca.* −0·3 v is, however, quite evident.

Because of the indeterminate position of its decomposition wave, it was not possible to identify the complex scandium ion in the manner used by Lingane (*loc. cit.*) for the biplumbite ion. The polarograph therefore merely provides confirmatory evidence of the formation of a scandate ion without, however, aiding its identification.

According to Cartledge (*J. Amer. Chem. Soc.*, 1928, **50**, 2855, 2863) the basicity, amphotericity, or acidity of a hydroxide is determined by the function $\sqrt{\phi}$ where ϕ is the ionic potential of the element. For scandium $\sqrt{\phi} = 2{\cdot}1$, indicating a basic hydroxide. Similarly, Sun (*J. Chinese Chem. Soc.*, 1937, **5**, 148) reports that elements yielding basic hydroxides have ϕ values $<6{\cdot}0$. The evidence is that scandium is anomalous in this respect in that it forms an amphoteric hydroxide. Since similar anomalies are known only where the element also forms ammino-complexes, the formation of amminoscandium compounds might be expected.

Precipitation of scandium hydroxide by aqueous ammonia was known by the earliest workers to be incomplete. Fischer and Bock (*loc. cit.*) attributed this to the presence of carbonates in the ammonia solution, but since incomplete precipitation is observed in a carbonate-free system, their contention cannot be tenable. Instead, the extent of precipitation can now be correlated with the ammonium-ion concentration. Precipitation of scandium hydroxide by ammonia is a complicated reaction and, when followed turbidimetrically (Fig. 1), is seen to require not only a slightly higher pH for its commencement, but is never so complete as with alkali hydroxide. Contrariwise, however, although the turbidimetric curve shows little indication of redissolution of precipitated scandium hydroxide even at high concentrations of ammonia, a fresh scandium hydroxide, washed free from other anions, can be partially redissolved in carbonate-free ammonia solution or by passing ammonia gas through its slurry. The ammoniacal solution, freed from excess of scandium hydroxide by filtration or centrifuging, can be freed from free ammonia (as shown by smell or litmus) by blowing carbon dioxide-free air or nitrogen through it. From such a de-ammoniated solution, scandium hydroxide is precipitated by the judicious addition of sodium hydroxide, and simultaneously ammonia is evolved. Further additions of sodium hydroxide redissolve the precipitated scandium hydroxide as previously indicated. NH_3 : Sc ratios in the ammine solution are very close to 6 : 1 (Table 2) which could correspond to a hexamminoscandium ion $[Sc(NH_3)_6]^{3+}$, the three positive charges being taken up in this instance by hydroxyl ions. The complex ammine, if such it be, does not appear to be very stable as evaporation of the solution causes decomposition with evolution of ammonia and precipitation of scandium hydroxide.

TABLE 2. *Composition of amminoscandium solutions.*

Sc_2O_3 (g.) obtained	NH_3 (g.) evolved	Ratio Sc : NH_3	Sc_2O_3 (g.) obtained	NH_3 (g.) evolved	Ratio Sc : NH_3
	Decomposed by NaOH.			*Decomposed by heat.*	
0·50	0·695	1 : 5·65	0·58	0·848	1 : 5·94
0·53	0·743	1 : 5·72	0·60	0·890	1 : 6·03
0·49	0·688	1 : 5·70	0·60	0·871	1 : 5·90

Scandium hydroxide also dissolves in solutions of ammonium chloride and nitrate, and these solutions are similarly decomposed by addition of sodium hydroxide.

Aluminium readily forms ammino-complexes (Klemm *et al.*, *Z. anorg. Chem.*, 1931, **200**, 343, 367), but those of the lanthanons are produced only under stringent conditions of temperature and pressure (Bergstrom, *J. Phys. Chem.*, 1925, **29**, 160; Huttig and Dauschau, *Monatsh.*, 1951, **82**, 742). It is to be expected that scandium and yttrium would display ammonia-co-ordinating tendencies intermediate between these two extremes. No data have been presented on the formation of amminoyttrium complexes, so this appears to be the first recorded production of " rare earth " ammino-complexes in aqueous solution.

A distinguishing feature of scandium solutions in ammonium or sodium hydroxide solutions lies in their behaviour on ion-exchange resins. Whereas scandium in ammoniacal or neutral ammine solution is readily adsorbed by a cation-exchange resin, and negligibly so on an anion-exchanger, the reverse is the case with solutions of scandium hydroxide in sodium hydroxide (see above).

EXPERIMENTAL

The scandium salts had been derived and purified as indicated in the preceding paper. Other reagents were generally of " AnalaR " grade. The tetramethylammonium salt used was the normal grade for polarographic work.

Turbidimetric titrations were made by means of a Parr photoelectric turbidimeter. pH determinations were made on a Cambridge electrometer, and polarography was conducted on a Tinsley pen-recording instrument with the supporting electrolytes at 0·1M-concentrations.

Adsorption of the scandate complex on ion-exchange resins was observed by shaking, for 48 hr., aliquot parts (200 ml.) of 0·05M-alkaline scandium solutions with Dowex-50 and Zeo-Karb

225 resins (100 g. each) in their sodium forms, and Amberlite IRA-400 and Deacidite FF resins in their fluoride forms. The scandium content of the mother-liquors was determined by adjustment of pH to 8·0, filtration and ignition of the precipitate to oxide. Control precipitation of the initial solution permitted quantitative comparison of the degree of absorption (Table 1).

Amminoscandium solutions were prepared as indicated earlier. Analyses were generally made by adding sodium hydroxide to the solution (to pH 8·2—8·8; Tropeolin OOO indicator), passing nitrogen through the solution, and boiling it to liberate the ammonia which was absorbed in standard acid in the usual way and thus determined. Scandium was determined by filtration and ignition of the precipitated hydroxide. Although precipitation of scandium hydroxide is now known to be incomplete, the ratios of Sc : NH_3 in the ammino-complex determined in this way are quite close to those determined by thermal decomposition (Table 2).

Acknowledgements are due to Mr. A. D. Dargaville for preparation of the polarograms.

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Scandium Oxalate and its Ammine Complexes.

By R. C. VICKERY.

[Reprint Order No. 5727.]

The preparation and solubilities are given of scandium oxalate with 3, 6, and 18 mols. of water of crystallisation. Absorption by scandium oxalate of water vapour, carbon dioxide, and ammonia is described. Adsorption of ammonia leads to the formation of $[Sc(NH_3)_6]_2(C_2O_4)_3$ complexes by replacement of co-ordinated water. The formation of anionic scandium oxalate complexes in solution is described.

SCANDIUM OXALATE can be obtained from solutions of scandium salts by the addition of oxalic acid but precipitation is never complete. Although its solubility in water has been confirmed as *ca.* 60 mg./l. (Fischer and Bock, *Z. anorg. Chem.*, 1942, **249**, 146) scandium oxalate does not appear to be precipitated from solutions containing <1·5 g. of Sc^{3+} per litre. Supersaturation may be partly responsible, but the relatively great solubility of scandium oxalate in acid and alkaline media, and in those containing alkali or ammonium ions, must be attributed to the extensive formation of complexes.

No crystallographic observations have appeared on scandium oxalate, but isomorphism with lanthanon oxalates is to be expected and the numerous hydrates reported suggest the existence of "interstitial" forms similar to those observed by Wylie for the lanthanons (*J.*, 1947, 1687). Minor quantities of alien ions grossly affect the nature of the precipitated oxalate (Sterba-Bohm and Skramowsky, *Coll. Czech. Chem. Comm.*, 1929, **1**, 1) and these, together with adsorbed ammonia and carbon dioxide (see below), may in part account for the various degrees of hydration reported. Scandium oxalate hexahydrate is readily prepared by precipitation from 5% solutions of scandium at *ca.* 60° (Klein and Bernays, *J. Amer. Chem. Soc.*, 1951, **73**, 1364), but absorption of ammonia or carbon dioxide by the oxalate has to be avoided. Klein and Bernays, and Sterba-Bohm and Skramowsky (*locc. cit.*) took pains to avoid such contamination without apparently appreciating the extent to which these gases are absorbed by scandium oxalate (see below). In an inert atmosphere, at temperatures up to *ca.* 90°, the hexahydrated oxalate is normally precipitated. An 18-hydrate has, however, been obtained by prolonged boiling of an oxalate suspension, whilst a trihydrate has been obtained by precipitation at 8°. On an oxide basis, water solubilities of these hydrates show insignificant variations from the confirmed data for the hexahydrate of Fischer and Bock, and Sterba-Bohm and Skramowsky (*locc. cit.*).

Data on the solubility of scandium oxalate were variously reported by Meyer and his co-workers (*Z. anorg. Chem.*, 1910, **67**, 398; 1914, **86**, 9) and Wirth (*ibid.*, 1914, **87**, 9), but the scandium employed by these early workers was somewhat adulterated by thorium. Solubilities now obtained for pure scandium oxalate are presented in the Table.

Solubility of scandium oxalate.

Solvent	Temp.	Hexahydrate	G./l. (as oxide)	Solvent	Temp.	Hexahydrate	G./l. (as oxide)
Water ...	25°	0·20	0·060	10% HNO_3	25°	27·4	8·17
			(trihydrate) 0·060	20%	25	58·2	17·36
			(18-hydrate) 0·061	10%	50	110·0	32·8
1% HCl	25	1·39	0·413	5% H_2SO_4	25	2·88	0·861
10%	25	25·25	7·54	15%	25	32·5	9·73
20%	25	46·5	13·87	5%	50	23·6	7·05
15%	60	72·4	21·6				

The influence of pH, alkali, and ammonium ions upon precipitation of scandium oxalate from M-scandium chloride solution is shown in Fig. 1. The ultimate upward trend of the alkali curve is attributed less to the precipitation of oxalate than to the precipitation of hydroxide, basic salts, or alkali scandium oxalate.

FIG. 1. *Recovery of* $Sc_2(C_2O_4)_3$ *at* pH *values varied by addition of* (*A*) NaOH, (*B*) *aqueous ammonia.*

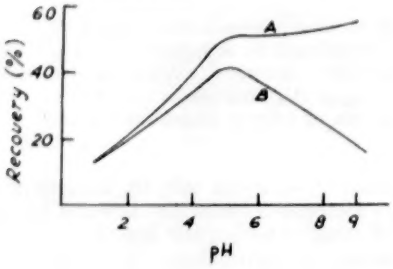
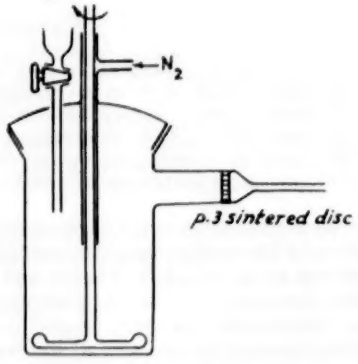


FIG. 2. *Apparatus for preparation of scandium oxalate in an inert atmosphere.*



Although earlier workers have been unable to agree upon the composition of various alkali scandium oxalates, available data support Wirth's suggestion (*ibid.*, p. 1) that in oxalate solution scandium forms an anionic complex of the type $[Sc(C_2O_4)_3]^{3-}$. Iron and aluminium form similar complexes, but Crouthamel and Martin (*J. Amer. Chem. Soc.*, 1950, **72**, 1382), in studying ytterbium oxalate complexes, decided that, whilst $[Yb(C_2O_4)_3]^{3-}$ was not formed in significant quantities, the complex necessarily carried a negative charge. Apart from variation of valency, many of the properties of scandium and ytterbium are closely analogous and it is to be expected that this may extend somewhat to the oxalates and their complexes. Experiments with ion-exchange resins give evidence for the formation of complex anions containing scandium and oxalate ions in the ratios 1 : 2·8 at pH 6·1 and 1 : 1·32 at pH 8·6, but insufficient additional results are available for further characterisation of the complexes.

Little attention appears to have been paid hitherto to the affinity of scandium oxalate for water vapour, ammonia, and carbon dioxide. Anhydrous scandium oxalate absorbs moisture quite readily, to form the trihydrate, but then, as with the 6- and the 18-hydrate, the oxalate is no longer deliquescent. Adsorption of carbon dioxide occurs only when the oxalate is moist; no definite composition levels appear to be reached, but 6% of carbon dioxide appeared to be the limit of adsorption, *i.e.*, $Sc^{3+} : C_2O_4^{2-} : CO_2 = 6 : 9 : 1$. Fischer

and Bock (*loc. cit.*) attributed the solubility of scandium oxalate in various solutions to the presence of carbonate ions; carbonated oxalates show a slight increase in solubility over normal oxalates, but the effect is much less than that with ammoniated oxalates.

When a small quantity of moist scandium oxalate hexahydrate, freshly precipitated in an inert atmosphere, is exposed to a large volume of ammonia vapour at *ca.* 25°, an anhydrous ammino-compound is formed containing scandium, ammonia, and oxalate ions in the ratio 2 : 12 : 3, *i.e.*, equivalent to $[Sc(NH_3)_6]_2(C_2O_4)_3$. This has close analogy to the ammino-compounds reported in the preceding paper, and can be construed as replacement of co-ordinated water by ammonia molecules.

Dry ammonia vapour is not absorbed by dry scandium oxalate, but the introduction of water vapour into the system immediately initiates exothermic reaction. Anhydrous oxalate in moist ammonia vapour absorbs 12 mols. of ammonia per mol. of oxalate. The 3- and the 18-hydrate, either moist or in a moist atmosphere, absorb ammonia up to the same level giving respectively anhydrous and 12-hydrated ammines.

Adequate determination of heat of ammination was prevented by lack of facilities, but, apart from qualitative tactile indications, a temperature rise of 10° was noted in one case of ammination of the anhydrous oxalate.

The great influence of ammonium ions upon the solubility of scandium oxalate (see above) was paralleled by the solubility of the solid ammine oxalates in water. Hexahydrated scandium oxalate, precipitated in an inert atmosphere and ammoniated whilst still moist on the filter, was readily soluble in cold water, giving a neutral solution. When heated, the solution decomposed with evolution of ammonia and precipitation of hexahydrated scandium oxalate. Similar decomposition occurred on the addition of sodium hydroxide.

The affinity of scandium oxalate for ammonia diminishes somewhat with age. This is particularly so with the anhydrous and hexahydrated salts, but rejuvenation is easily affected by boiling the oxalate in water for a short time.

Ammination of scandium oxalate throws additional light on the nature of its hydrates. Co-ordination of six ammonia molecules to one scandium ion by the obvious displacement of 6 mols. of water can only mean that the latter were previously co-ordinated to the scandium and were neither interstitial in nature nor mere attributes of crystal formation. No displacement of unco-ordinated water occurs, as shown by ammination of the 18-hydrate, so the probability is increased that twelve water molecules in the 18-hydrate are present interstitially.

The presence of moisture as a prerequisite to ammination even of the hydrated oxalate represents but a further example of aquo-catalysis.

Experimental

The scandium was that derived from wolframite residues and thortveitite as described by Vickery (*J.*, 1954, 245). "AnalaR" oxalic acid was recrystallised once before use. Other reagents were of similar standard. Nitrogen, carbon dioxide, and ammonia were all of normal cylinder quality and were dried before use.

Precipitation and filtration of scandium oxalate in an inert atmosphere was effected in the apparatus shown in Fig. 2. Early attempts to influence the degree of hydration by variation of concentration of reagents were unsuccessful but did show the minimum concentration of scandium which could be precipitated by oxalic acid to be 1·5 g./l.

Oxalate solubilities in the media given in Table 1 were obtained by sealing 0·5 g. of oxalate in a glass tube with 15—20 ml. of solvent. The sealed tubes were shaken continuously in a thermostat for 3½ days, then left stationary in the thermostat for 1½ days. Before the tubes were opened the residual oxalate was centrifuged at high speed for 30 min. 10 ml. of solution were cautiously evaporated to dryness in a weighed platinum dish under infra-red lamps, and the residue was moistened with 1—2 drops of sulphuric acid, re-evaporated, ignited at 1200° for 30 min., and weighed. Oxide weights were converted back into the appropriate oxalate hydrate.

Data for the curves in Fig. 1 were obtained by igniting and weighing as oxide the scandium oxalate precipitated from solutions containing quantities of scandium under the conditions given.

The anionic nature of the oxalate complex in solution was observed by equilibrating portions (50 ml.) of scandium oxalate solution with 10 g. each of Dowex-50 resin (hydrogen form) and Amberlite IRA-400 resin (chloride form). Negligible adsorption of scandium occurred on the cation-exchange but 82% was taken up by the anionic-exchange resin. A short series of experiments was then made in which 200-ml. portions of scandium oxalate solution each containing 200 mg. of Sc_2O_3 [668 mg. of $Sc_2(C_2O_4)_3,6H_2O$] were adjusted, by addition of sodium hydroxide solution, to pH 6—8. These were then shaken for 24 hr. with Amberlite IR-100 resin (50 g.); the resin was filtered off and washed with cold distilled water, and the scandium oxalate complex leached out with 5% sulphuric acid (200 ml.). The scandium content of this eluate was determined by direct evaporation and ignition; oxalate was determined by permanganate titration. Results (mg./200 ml. of eluate) were:

pH	6·1	6·9	7·5	8·0	8·6
Sc_2O_3	164	153	174	163	182
$H_2C_2O_4$	306	231	218	165	160
$Sc^{3+}:C_2O_4^{2-}$	1 : 2·8	1 : 2·25	1 : 1·87	1 : 1·51	1 : 1·32

Adsorption of ammonia by moist scandium oxalate was first observed during metathesis by sodium hydroxide of a scandium oxalate precipitate which had remained for several hours on a filter paper in the laboratory atmosphere. When the oxalate was reconstituted with water and the alkali added, an odour of ammonia was noticed. Subsequently ammination of the oxalate was effected by passing ammonia gas through a slurry of the oxalate or over a thin layer of moist oxalate held in a flat Vitreosil dish.

For the preparation of the anhydrous ammine *oxalate*, the hexahydrated oxalate was first precipitated and filtered off under nitrogen (apparatus: Fig. 2). The nitrogen flow was then replaced by ammonia. Dehydration of the scandium oxalate filter cake was rapid and obvious. After 15 minutes' ammoniation, nitrogen was passed through the apparatus which was then opened and the solid ammino-oxalate extracted. Ammonia in the solid was determined by treatment with alkali and absorption of the liberated ammonia in standard acid. Scandium was determined by direct ignition to oxide, and oxalate by permanganate titration in acid solution {Found: Sc_2O_3, 25·2; $(C_2O_4)^{2-}$, 47·0; NH_3, 36·1. $[Sc(NH_3)_6]_2(C_2O_4)_3$ requires Sc_2O_3, 24·6; $(C_2O_4)^{2-}$, 47·3; NH_3, 36·6%}. The 3- and the 18-oxalate hydrates prepared as indicated above were ammoniated by passing ammonia over samples of these hydrates in Petri dishes in a larger glass container. After 4 hours' exposure, samples gave analyses: *3-Hydrate:* Sc_2O_3, 24·9; $(C_2O_4)^{2-}$, 47·0; NH_3, 36·2. $[Sc(NH_3)_6]_2(C_2O_4)_3$ requires Sc_2O_3, 24·6; $(C_2O_4)^{2-}$, 47·3; NH_3, 36·6. *18-Hydrate:* Sc_2O_3, 17·5; $(C_2O_4)^{2-}$, 34·0; NH_3, 26·7; loss on ign., 82·5. $[Sc(NH_3)_6]_2(C_2O_4)_3,12H_2O$ requires Sc_2O_3, 17·8; $(C_2O_4)^{2-}$, 34·1; NH_3, 26·4; loss on ign., 82·2%.

Ammination of anhydrous scandium oxalate was effected by first dehydrating the trihydrate at 150° for 18 hr. and then passing over the solid a stream of ammonia obtained by blowing carbon dioxide-free air through carbon dioxide-free ammonia solution and then over the oxalate. A thermometer in the body of the anhydrous oxalate showed a rapid rise in temperature of the solid (20 g.) from 18° to 28° in the first five minutes of ammoniation; thereafter the temperature decreased throughout the ammination.

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Studies on Specific Chemical Fission of Peptide Links. Part I. The Rearrangement of Aspartyl and Glutamyl Peptides.

By Alan R. Battersby and J. C. Robinson.

[Reprint Order No. 5736.]

The esters of α- and β-aspartyl peptides (types II and X; $n = 1$) have been converted by alkaline hydrolysis into mixtures of acidic aspartyl peptides of types (V) and (VI). In all cases studied, the former product preponderates. The rearrangement has been shown to occur by cyclisation to the related imides (IV) followed by hydrolysis. Esters of glutamyl peptides are rearranged in a similar way, but certain differences from the aspartyl analogues have been discovered. The possible application of this rearrangement in a scheme for the specific fission of a peptide chain at the aspartic and glutamic residues is discussed.

A peptide may be degraded for structural study by partial hydrolysis with acids or enzymes, or by stepwise removal of amino-acid residues from the ends of the chain. Advances in these fields were reviewed in 1952 by Khorana (*Quart. Reviews*, **6**, 340) and several more recent contributions have been made (*e.g.*, Boissonnas, *Helv. Chim. Acta*, 1952, **35**, 2226; Holley and Holley, *J. Amer. Chem. Soc.*, 1952, **74**, 5445; Kenner, Khorana, and Stedman, *J.*, 1953, 673). Since the structure of a small peptide is more readily elucidated by these methods than that of a large one, it is desirable that chemical methods should be devised for the fission of a peptide chain at known points along its length. A satisfactory method must give a high yield of fission products under mild conditions. The avoidance of racemisation at the α-carbon atoms of the amino-acid residues would be an advantage, but this is not of paramount importance for most degradative studies.

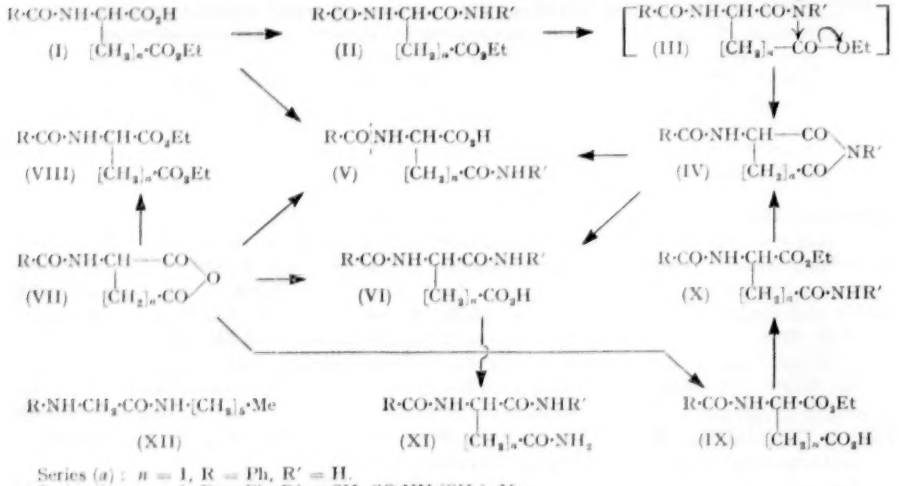
The only work along these lines seems to be that of Elliott (*Biochem. J.*, 1952, **50**, 542) who studied the specific hydrolysis of the peptide links of serine in silk fibroin. In our case, the initial effort has been directed towards a fission of the peptide chain at those points where aspartic or glutamic acid residues occur.

The first step of one scheme we envisaged, as briefly reported earlier (*Chem. and Ind.*, 1954, 45), involves the rearrangement of the normal α-aspartyl and α-glutamyl peptides (VI; $n = 1$ and 2) to give the β- and γ-isomers (V; $n = 1$ and 2) respectively. The latter possess the group $\cdots CO{\cdot}NH{\cdot}CHR{\cdot}CO_2H$ which differs from the carboxyl end of a peptide chain only in the nature of the group R. These peptides should therefore be susceptible to specific fission as indicated in (V) by use of one of the methods developed for selective removal of the *C*-terminal residue (Khorana; Boissonnas; Kenner, Khorana, and Stedman, *locc. cit.*). This second step will be the subject of a later communication.

Imides of type (IV) are the obvious intermediates for the required rearrangement, and their ready hydrolysis under mild alkaline conditions is well known (Titherley and Stubbs, *J.*, 1914, **105**, 299). It remained to establish that the desired hydrolysis product of type (V) was obtained in satisfactory yield. Cherbuliez and Chambers (*Helv. Chim. Acta*, 1925, **8**, 395) showed that hydrolysis of DL-benzamidosuccinimide (IV*a*) with hot saturated barium hydroxide affords *N*-benzoyl-DL-asparagine (V*a*) but the yield was not recorded. These conditions are unnecessarily drastic and we therefore hydrolysed (IV*a*) with cold dilute sodium hydroxide or equally effectively with warm 0·28N-sodium carbonate. Almost a quantitative yield was obtained of a product which was mainly the desired benzoylasparagine (V*a*), though a small amount of *N*-benzoyl-DL-*iso*asparagine (VI*a*) was also isolated. The latter was prepared for comparison by the action of ammonia on *N*-benzoyl-DL-aspartic anhydride (VII*a*) (cf. Pauly and Weir, *Ber.*, 1910, **43**, 661). Again a mixture of the two amides (V*a*) and (VI*a*) resulted, the latter preponderating. The relative amounts of (V*a*) and (VI*a*) obtained by ring-opening of the imide (IV*a*) and the anhydride (VII*a*) with hydroxyl ion and ammonia, respectively, must be governed, at least in part, by the relative electrophilic character of the two carbonyl groups in the ring. In the absence of

overpowering steric hindrance, attack at the α-carbonyl group (corresponding to the stronger carboxyl group) should be favoured, in accord with the results above and others given below (cf. Emery and Gold, *J.*, 1950, 1455).

Cherbuliez and Chambers (*loc. cit.*) prepared the imide (IV*a*) by heating benzoylasparagine at 200° and, as a by-product, they isolated an impure substance, m. p. 245—250°, which gave roughly the analysis for *N*-benzoyl-DL-aspartic diamide (XI*a*). We have now purified this material, m. p. 270—271°, and have confirmed the structure (XI*a*) by direct comparison with a specimen made from the imide (IV*a*) and ammonia. The drastic



Series (*a*): $n = 1$, R = Ph, R′ = H.
Series (*b*): $n = 1$, R = Ph, R′ = CH_2·CO·NH·[CH_2]$_5$·Me.
Series (*c*): $n = 2$, R = Ph, R′ = H.
Series (*d*): $n = 2$, R = Ph, R′ = CH_2·CO·NH·[CH_2]$_5$·Me.
Series (*e*): $n = 2$, R = CH_2Ph·O·CO·NH·CH_2·CO·NH·CH_2, R′ = CH_2·CO·NH·[CH_2]$_5$·Me.
Series (*f*): $n = 2$, R = NHAc·CH_2·CO·NH·CH_2, R′ = CH_2·CO·NH·[CH_2]$_5$·Me.

and evidently complex nature of the above preparation of imides makes it valueless for our present purpose. Attempts were therefore made to cyclise *N*-benzoyl-DL-*iso*asparagine ethyl ester (II*a*) under acidic conditions (see p. 264) but without success. A suitably mild method was discovered, however, when the action of 0·5 equiv. of dilute sodium hydroxide on the ester (II*a*) gave 43% of the imide (IV*a*); the latter was also formed when (II*a*) reacted with sodium ethoxide in ethanol. These reactions are probably initiated by removal of a proton to give (III*a*), followed by cyclisation. When an excess of cold 0·1N-sodium hydroxide or warm 0·28N-sodium carbonate was used, ring-closure of (II*a*) and subsequent hydrolysis of the imide were accomplished in one stage. A mixture of the asparagine (V*a*) and *iso*asparagine (VI*a*) derivatives was obtained, which was shown by fractionation on IR-4B resin to contain some 65% of the former.

In order to be sure that all the benzoylasparagine (V*a*) had been produced by rearrangement during the alkaline hydrolysis of (II*a*), it was necessary to prove that the supposed β-ethyl *N*-benzoyl-DL-aspartate (I*a*) used for the preparation of (II*a*) was in fact free from the α-ethyl isomer (IX*a*). The possibility of rearrangement in the conversion of the ester (I*a*) into (II*a*) by the mixed anhydride method (Boissonnas, *Helv. Chim. Acta*, 1951, **34**, 874; Vaughan, *J. Amer. Chem. Soc.*, 1951, **73**, 3547; Wieland and Bernhard, *Annalen*, 1951, **572**, 190) had also to be eliminated. First, the ester (I*a*) gave a good yield of benzoylasparagine (V*a*) when treated with aqueous ammonia. For further evidence, α-ethyl *N*-benzoyl-DL-aspartate (IX*a*) was prepared, in admixture with the β-isomer (I*a*) and the diethyl ester (VIII*a*), by heating *N*-benzoyl-DL-aspartic anhydride with ethanol. The α-ester was isolated almost pure by fractional extraction (Le Quesne and Young, *J.*, 1950, 1954) and was completely purified by countercurrent distribution (Craig and Craig,

" Technique of Organic Chemistry," Ed. by Weissberger, Interscience Publ., New York, 1950, Vol. III, p. 171). That our preparation of the β-ester (I*a*) was quite free from the α-ester (IX*a*) was shown by countercurrent distribution of the former alone and in admixture with the latter. A single peak was obtained in the first case and two in the second. Both pure isomers (I*a*) and (IX*a*) were converted by the mixed anhydride method into the corresponding amido-esters which were different and homogeneous and must be (II*a*) and (X*a*) respectively. Thus, rearrangement has not occurred by way of the mixed anhydrides but only in the treatment of the ester (II*a*) with bases. In this simple case, the desired conversion of an α-aspartyl " peptide " into the β-isomer has been achieved in good yield under mild conditions.

The ethyl esters (II*b*) and (X*b*) of *N*-benzoyl-α- and -β-DL-aspartylglycine *n*-hexylamide were prepared from (I*a*) and (IX*a*) respectively, by the mixed anhydride method using ethyl chloroformate and glycine *n*-hexylamide (XII; R = H). A by-product from these preparations was shown to be ethoxycarbonylglycine *n*-hexylamide (XII; R = CO_2Et) which could arise either by attack at the second carbonyl group of the mixed anhydride or from any ethyl chloroformate present in the reaction mixture as a result of incomplete mixed anhydride formation. The two esters (II*b*) and (X*b*) with warm aqueous sodium carbonate solution both gave mixtures of the isomeric acidic peptides (V*b*) and (VI*b*), which were readily separated by countercurrent distribution. The component which made up about 75% of each mixture was assigned the structure (V*b*) because it had a lower partition ratio than its isomer in the buffered solvent system and must be the stronger acid. This assignment was confirmed by acidic hydrolysis (Sheehan, Chapman, and Roth, *J. Amer. Chem. Soc.*, 1952, **74**, 3822) of the ester (II*b*), of unequivocal structure, to give (VI*b*), which was identical with the weaker acid obtained from the alkaline hydrolysis. Thus both esters are rearranged by alkali and the fact that they yield mixtures of much the same composition suggests that simple hydrolysis of the ester group is not a serious side reaction in the aspartic acid series. When the reaction with sodium carbonate was stopped before completion, the neutral product from both esters was the imide (IV*b*); hydrolysis of the imide is therefore the rate-controlling reaction. Finally, the structures of the acidic peptides (V*b*) and (VI*b*) were confirmed by synthesis from *N*-benzoyl-DL-aspartic anhydride and glycine *n*-hexylamide; the weaker acid (VI*b*) predominated in the product.

The asparaginyl peptide (XI*b*), prepared from the related acid (VI*b*) by way of the mixed (carbonic) anhydride, was largely unaffected by cold 0·1N-sodium hydroxide or warm 0·25N-sodium carbonate. The main part of the small amount of acidic material which was obtained was the rearranged peptide (V*b*).

In the glutamic acid series, *N*-benzoyl-α-DL-glutamylglycine *n*-hexylamide ethyl ester (II*d*) was more resistant to warm aqueous sodium carbonate solution than the aspartyl analogue (II*b*): 64% of the former ester was unchanged even after 7 hours. This difference in reactivity may be a valuable one. The glutamyl peptide was hydrolysed almost completely, however, by 0·1N-sodium hydroxide at room temperature to give a mixture of two acidic peptides, separable by countercurrent distribution. The main product (57%) was assigned the structure (V*d*) and the second product the structure (VI*d*) by the argument used in the aspartic acid series; the synthesis of these acidic peptides from *N*-benzoyl-DL-glutamic anhydride (VII*c*) and glycine *n*-hexylamide followed our earlier work on the aspartyl analogues. It is interesting that the yield of rearranged product from (II*d*) is appreciably lower than that from the aspartyl analogue (II*b*). One or both of the following factors may be involved: (*a*) the desired hydrolysis of the intermediate imide (IV*d*) to give (V*d*) is only slightly favoured over the alternative direction of ring-opening; (*b*) simple hydrolysis of the ester group in (II*d*) competes significantly with the ring-closure reaction. Further work is necessary on this point. In any case, esterification of the weaker acid (VI*d*) and treatment again with alkali would afford a better overall yield of the desired acid (V*d*). Clayton and Kenner (*Chem. and Ind.*, 1953, 1205) have briefly reported the conversion of a α-glutamyl peptide into the γ-isomer by a different method.

In the hydrolysis of (II*d*) with sodium hydroxide, a trace of neutral material was isolated and shown to be the unchanged ester; ring-closure to the imide is therefore the rate-

controlling step in contrast to the cases in the aspartic acid series. This is in accord with Sircar's observation (*J.*, 1927, 1252) that glutarimide is hydrolysed more readily than succinimide. It is not surprising then that our attempts to isolate the imide (IV*d*) were unsuccessful.

Finally, a study was made of the alkaline hydrolysis of the ethyl ester of an optically active peptide, *N*-acetylglycylglycyl-α-L-glutamylglycine *n*-hexylamide (II*f*). The main acidic product, optically inactive within the limits of experimental error, was assigned the structure (V*f*), *i.e.*, the rearranged product, because of its acidic strength (pK_a 3·45). This was confirmed by anodic oxidation of the main product in anhydrous methanol (Boissonnas, *Helv. Chim. Acta*, 1952, **35**, 2226) followed by complete hydrolysis of the oxidation products. Chromatography of the hydrolysate showed that the glutamic acid had been almost completely destroyed without the formation of a new amino-acid. In this it resembled the behaviour of the acid (V*d*) and differed from the acid (VI*d*) which were similarly oxidised for comparison. In the latter case, the glutamic acid was not completely destroyed and a new substance, probably α-amino-γ-methoxybutyric acid, was present in the hydrolysate. A minor acidic product, isomeric with (V*f*) but different from it, was also isolated from the alkaline hydrolysis of (II*f*); this product is probably the weaker acid (VI*f*) but the small quantity available and its awkward solubility properties precluded satisfactory identification.

It seems probable that the rearrangement described above is a general one for those esters of unsymmetrical succinamic and glutaramic acids which are capable of forming imides. Indeed, independently of our work, Hancock and Linstead (*J.*, 1953, 3490) observed rearrangement during alkaline hydrolysis of the anilic esters of methylsuccinic acid. More recently, Sondheimer and Holley (*J. Amer. Chem. Soc.*, 1954, **76**, 2467) have published other examples similar to ours in the amino-acid series. Syntheses involving alkaline hydrolysis of substances of this general type must therefore be used with care. For example, it seems likely that the acidic product obtained by alkaline hydrolysis of the polyester of α-polyglutamic acid (Bruckner, K. Kovács, J. Kovács, and Kótai, *Experientia*, 1954, **10**, 166) will contain an appreciable amount of γ-linked material.

Experimental

Analyses are mainly by Mr. B. S. Noyes of Bristol. Analytical samples were dried at 100° *in vacuo* over phosphoric oxide, unless otherwise stated. Evaporations were carried out at 40° under reduced pressure. Congo-red was the indicator used for acidifications, unless otherwise stated.

β-Ethyl N-Benzoyl-DL-aspartate (I*a*).—A solution of β-ethyl DL-aspartate hydrochloride (9·9 g., 0·05 mole) (Piutti, *Gazzetta*, 1888, **18**, 480; cf. Coleman, *J.*, 1951, 2294) and anhydrous potassium carbonate (10·4 g., 3 equiv.) in water (40 ml.) was stirred vigorously at 0° whilst benzoyl chloride (7 g.) in dioxan (20 ml.) was added during 1·5 hr. After being stirred for a further 2 hr. at 0°, the solution was made alkaline with potassium carbonate (0·3 g.) and extracted with ether (3 × 100 ml.). The aqueous layer was acidified and extracted with ethyl acetate (3 × 100 ml.). The latter extract, after being washed with water, dried, and evaporated, yielded a pale yellow gum (13·1 g.). When crystallised from 10% aqueous ethanol (300 ml.), this product gave *β-ethyl N-benzoyl-DL-aspartate* (9·99 g., 75%), m. p. 104—105°. A sample recrystallised twice from the same solvent gave diamond-shaped plates, m. p. 105—107° (Found: C, 58·9; H, 5·6; N, 5·0. $C_{13}H_{15}O_5N$ requires C, 58·9; H, 5·7; N, 5·3%). A portion of the final product was fractionated by countercurrent distribution (30 transfers) between ethyl acetate and aqueous phosphate buffer made from 0·5M-KH_2PO_4 (20 vol.) and 0·5M-K_2HPO_4 (1 vol.). One slightly skewed peak (partition ratio K 0·7) was obtained, indicating the presence of a single component for which K increases with increasing concentration. The presence of two components in a mixture of the β-ethyl ester (I*a*) and the α-ethyl ester (IX*a*) (K 2·2) was clearly visible after 30 transfers in the same solvent system.

γ-Ethyl N-Benzoyl-DL-glutamate (I*c*).—γ-Ethyl DL-glutamate, m. p. 187—188° (decomp.) (King and Spensley, *J.*, 1950, 3159), was prepared in 75% yield by the procedure used by Miller and Waelsch (*Arch. Biochem. Biophys.*, 1952, **35**, 176) for the L-isomer. The DL-ester (3 g.) was benzoylated and the product was crystallised as above to give *γ-ethyl N-benzoyl-*

DL-*glutamate* (3·21 g., 67%) as colourless needles, m. p. 112—114°, raised to 114—115·5° by recrystallisation twice from 10% aqueous ethanol (Found: C, 59·8; H, 6·0; N, 4·7%; equiv., 278. $C_{14}H_{17}O_5N$ requires C, 60·2; H, 6·1; N, 5·0%; equiv., 279).

N-*Benzoyl*-DL-*isoasparagine Ethyl Ester* (II*a*).—A stirred solution of the acid (I*a*) (5·3 g.) and triethylamine (2·8 ml.) in dioxan (250 ml.) and chloroform (50 ml.) was treated at 0° with ethyl chloroformate (2 ml.). An excess of aqueous ammonia (4 ml.; *d* 0·880) was added after 20 min. and stirring was continued for 5 hr. while the reaction mixture warmed to room temperature. After addition of water (50 ml.), the solution was made just acid to litmus and was evaporated to 50 ml.; the addition of water and evaporation were repeated. The resultant suspension was adjusted to pH 8 with potassium carbonate, and the solid collected and resuspended in 0·01N-hydrochloric acid. The insoluble *ethyl ester* (II*a*) (4·44 g., 83%), m. p. 149—150°, was collected and washed with water. One recrystallisation from 10% aqueous ethanol gave plates, m. p. 151—153°, unchanged by recrystallisation (Found: C, 59·3; H, 6·3; N, 10·2. $C_{13}H_{16}O_4N_2$ requires C, 59·1; H, 6·1; N, 10·6%).

Action of Ammonia on N-*Benzoyl*-DL-*aspartic Anhydride*.—A stream of dry ammonia was passed into a solution of the anhydride (3·6 g.) (Lawson, *J.*, 1953, 1046) in warm dry dioxan (160 ml.) until no further precipitate formed. The gummy ammonium salts, freed from dioxan by decantation, were dissolved in water (50 ml.), and the solution was acidified. A mixture of *N*-benzoyl-DL-asparagine (V*a*) and *N*-benzoyl-DL-*iso*asparagine (VI*a*) separated (3·94 g.), having m. p. 199—200° after sintering (Found, for mixture: equiv., 238. Calc.: equiv., 236). The whole crop was dissolved in 0·2N-sodium carbonate (90 ml., 1·1 equiv.) and portions of 1·15N-hydrochloric acid (11·7, 2·25, 5 ml.) were added to precipitate three fractions (2·32 g., m. p. 205—206°; 0·524 g., m. p. 194—196° after sintering from 180°; 0·591 g., m. p. 188—190°, respectively). The last was almost pure benzoylasparagine and melted at 189—190° in admixture with an authentic sample. The first fraction was again dissolved in aqueous sodium carbonate (1 equiv.), and hydrochloric acid (0·5 equiv.) was added; N-*benzoyl*-DL-*isoasparagine* separated as needles, m. p. 208—209°, unchanged by recrystallisation from 10% aqueous ethanol (Found, in material dried at 110°: C, 55·8; H, 5·2; N, 12·0%; equiv., 243. $C_{11}H_{12}O_4N_2$ requires C, 55·9; H, 5·1; N, 11·9%; equiv., 236). This amide was recovered unchanged (90%) after being warmed for 3 hr. at 50—60° with 0·28N-sodium carbonate (3 equiv.).

N-*Benzoyl*-DL-*asparagine* (V*a*).—(a) *From* β-*ethyl* N-*benzoyl*-DL-*aspartate*. A solution of the ester (I*a*) (0·61 g.) in aqueous ammonia (40 ml.; *d* 0·880) was warmed at 40° for 3 days and then evaporated to dryness. The residue was dissolved in water (15 ml.) and acidified, *N*-benzoyl-DL-asparagine separating (0·51 g.), m. p. 184—186° raised to 191—192° by one recrystallisation from water. Cocker (*J.*, 1940, 1489) records m. p. 190—191°. Mixtures of this product with up to 30% of *N*-benzoyl*iso*asparagine melted at *ca.* 190—192°, after sintering; higher proportions of the *iso*asparagine raised the m. p., *e.g.*, 40% of the *iso*asparagine (VI*a*) with 60% of the asparagine derivative (V*a*) melted at 192·5—193°.

(b) *Racemisation of* N-*benzoyl*-L-*asparagine*. A solution of the L-amide (8·8 g.) (Pauly and Weir, *loc. cit.*) in water (53 ml.) was adjusted to pH 8 with sodium carbonate and then stirred with acetic anhydride (53 ml.) for 36 hr. without external cooling. Evaporation of the solution left a gum which was dissolved in water (50 ml.) and acidified. *N*-Benzoyl-DL-asparagine separated (8·3 g.), had m. p. 184—185°, raised by one recrystallisation from water to 191—192° alone or in admixture with the foregoing product (cf. Barker, *J.*, 1953, 453). A solution (*c*, 10·8) of the product in water containing ammonia (2 equiv.) was optically inactive.

N-*Benzoyl*-DL-*aspartic Acid Diamide* (XI*a*).—A solution of DL-benzamidosuccinimide (0·148 g.) in aqueous ammonia (10 ml.; *d* 0·880) deposited the *diamide* (0·13 g., 88%), m. p. 270—271° (decomp.), during 20 hr. at room temperature. Recrystallised from water, the diamide formed colourless needles (Found: C, 56·3; H, 5·6; N, 17·6. $C_{11}H_{13}O_3N_3$ requires C, 56·2; H, 5·6; N, 17·8%).

DL-*Benzamidosuccinimide* (IV*a*).—(a) *From* N-*benzoyl*-L-*asparagine*. Cherbuliez and Chambers's method (*loc. cit.*) yielded the two fractions described by them. One, sparingly soluble in ethanol, had m. p. 225—245°, raised by recrystallisation thrice from water to 268—269° alone or in admixture with the foregoing product. The second fraction, moderately soluble in ethanol, consisted of very crude imide (IV*a*) which in our hands could only be partly purified by repeated crystallisation from ethanol (cf. *idem*, *loc. cit.*). This fraction was therefore powdered finely and dissolved *rapidly* at room temperature in a slight excess of 0·25N-sodium carbonate, and the filtered solution was immediately adjusted to pH 7·5. Almost pure imide crystallised as prisms (3·5 g., 38%), m. p. 223—225°, raised by one recrystallisation from ethanol

to 224—225°. Cherbuliez and Chambers (*loc. cit.*) record m. p. 225—226°. *N*-Benzoyl-DL-*iso*-asparagine was cyclised in the same way to give the imide (IV*a*).

(b) *By the action of sodium hydroxide on* N-*benzoyl*-DL-iso*asparagine ethyl ester.* This ester (0·528 g.) was treated in ethanol (15 ml.) at room temperature with N-sodium hydroxide (1 ml., *ca.* 0·5 equiv.) and, after 18 hr., with 1·15N-hydrochloric acid (1·1 ml.). The alcohol was evaporated, water (10 ml.) added, and the resultant suspension brought to pH 7·5 with sodium carbonate. The neutral fraction (0·239 g.), m. p. 219—220° (after sintering), was collected, washed with water, and recrystallised from ethanol to give the imide (IV*a*) (0·189 g., 43%), m. p. 224—225° alone or in admixture with the foregoing product (Found, in material dried at 110°: C, 60·4; H, 4·7; N, 12·4. Calc. for $C_{11}H_{10}O_3N_2$: C, 60·5; H, 4·6; N, 12·8%).

(c) *By the action of sodium ethoxide on* N-*benzoyl*-DL-iso*asparagine ethyl ester.* A solution of the amido-ester (0·132 g.) in absolute ethanol (15 ml.) was warmed at 50° with sodium ethoxide (0·1 equiv.) for 8 hr. and then set aside for 30 hr. at room temperature. 0·1N-Hydrochloric acid (1 ml.) was added, and the solution evaporated to dryness. The crystalline residue was separated by partition as usual between ethyl acetate and aqueous sodium hydrogen carbonate into an acidic and a neutral fraction. The latter (0·121 g.), which flowed partly at 140—145° and was completely molten at 200°, was dissolved in hot water (20 ml.), and the cooled solution was filtered. An excess of silver nitrate (0·1 g.) was added to the filtrate, followed by dropwise addition of aqueous sodium carbonate solution until the immediate precipitation of white solid ceased. The silver derivative was collected, washed with water, and treated with dilute nitric acid; a clear solution was obtained which rapidly deposited crystals of the imide (IV*a*) (21 mg., 19%), m. p. 224—225° alone or in admixture with the foregoing product.

Attempts to cyclise benzoyl-DL-*iso*asparagine to the imide (IV*a*) with acetic anhydride at 100° were unsuccessful. *N*-Benzoyl-DL-*iso*asparagine ethyl ester was recovered unchanged after being heated at 180—190° for 0·5 hr.

Diethyl N-*Benzoyl*-DL-*aspartate* (VIII*a*).—*N*-Benzoyl-DL-aspartic acid (1 g.) (Cocker, *loc. cit.*) was treated in absolute ethanol (20 ml.) with dry hydrogen chloride and then heated under reflux for 1 hr. The *diester* (1·04 g., 84%), isolated in the usual way, crystallised from ether–light petroleum as rosettes of needles, m. p. 75—77° unchanged by recrystallisation (Found, in sample dried at 65°: C, 61·6; H, 6·5; N, 4·9. $C_{15}H_{19}O_5N$ requires C, 61·4; H, 6·5; N, 4·8%).

α-*Ethyl Hydrogen* N-*Benzoyl*-DL-*aspartate* (IX*a*).—*N*-Benzoyl-DL-aspartic anhydride (2·1 g.) in absolute ethanol (50 ml.) was heated under reflux for 3 hr. The gum recovered by evaporation of the solution was dissolved in ether and shaken with 0·28N-sodium carbonate (3 × 9 ml., finally with 20 ml.). The ether was dried and evaporated to leave a gum (0·214 g.) which crystallised from ether–light petroleum to give the diethyl ester (VIII*a*), m. p. 75—77° alone or in admixture with the foregoing product.

The four alkaline extracts when acidified precipitated oils, of which all save that from the first extract gradually crystallised; the solids from the second, third, and fourth extracts were collected separately (0·43 g., m. p. 103—104°; 0·566 g., m. p. 104—105°; 0·283 g., m. p. 104—106°, respectively). The combined crystalline product was freed from the β-ethyl isomer (I*a*) by countercurrent distribution (58 transfers) between ethyl acetate and the phosphate buffer described on p. 263. The solutions from tubes 38—51 were combined, and the separated aqueous layer was acidified and thoroughly extracted with ethyl acetate. After being washed with water, the upper layer from these tubes and the extracts were dried and evaporated to a gum (1·0 g.). This crystallised from water to give the α-*ethyl hydrogen ester* as prisms (0·785 g.), m. p. 111—112·5° (Found: C, 58·8; H, 5·7; N, 5·3. $C_{13}H_{15}O_5N$ requires C, 58·9; H, 5·7; N, 5·3%); the mixed m. p. with β-isomer (I*a*) was 80—95°.

N-*Benzoyl*-DL-*asparagine Ethyl Ester* (X*a*).—This was prepared on a 1 mmol. scale as for its isomer (II*a*) save that dioxan (22 ml.) and chloroform (4 ml.) were used to obtain a clear solution. The neutral products were extracted into ethyl acetate (total 110 ml.), and the extract was washed with water, dried, and evaporated to leave a white solid (0·208 g., 80%). Recrystallised from water, it yielded N-*benzoyl*-DL-*asparagine ethyl ester* as rosettes of long needles, m. p. 152—154° (Found: C, 59·3; H, 6·2; N, 10·4. $C_{13}H_{16}O_4N_2$ requires C, 59·1; H, 6·1; N, 10·6%). In admixture with its isomer (II*a*) the m. p. was 132—149°.

Attempted Cyclisation of Benzoyl-DL-iso*asparagine Ethyl Ester* (II*a*) *under Acidic Conditions.*—(*a*) A solution of anhydrous (II*a*) (0·1 g.) in anhydrous nitromethane (10 ml.) was treated with a slow stream of dry hydrogen bromide at 0° for 1 min. After being kept at room temperature in the dark for 16 hr., the yellow solution had deposited crystals (71 mg.) shown to be ammonium and/or methylamine hydrobromide derived from the nitromethane (cf. Albertson and McKay,

J. Amer. Chem. Soc., 1953, **75**, 5323). The nitromethane solution was evaporated to dryness and the residue was partitioned between aqueous sodium hydrogen carbonate and ethyl acetate. The neutral fraction (84 mg.) was very soluble in ethanol (1 ml.) and did not crystallise on seeding with the imide (IV*a*).

(*b*) Dry hydrogen chloride was bubbled for 5 min. into a solution of the ester (II*a*) (0·1 g.) in absolute ethanol (35 ml.) at 0°. After being kept for 16 hr. at room temperature, the solution was evaporated to a gum which was separated into two fractions by treatment with ether. One, readily soluble (40 mg.), was the crude diethyl ester (VIII*a*), m. p. 70·5—72·5° raised to 72·5—74·5° in admixture with an authentic sample. The second, sparingly soluble (39 mg.), was a mixture of ammonium chloride and starting material.

Action of Bases on DL-*Benzamidosuccinimide* (IV*a*).—A solution of the imide (0·436 g.) in 20% aqueous ethanol (20 ml.) was treated with N-sodium hydroxide (2·1 ml., 1·05 equiv.) and kept for 16 hr. at room temperature. After extraction with ethyl acetate (3 × 50 ml.) to remove neutral matter (28 mg.), the solution was adjusted to pH 7·5 with hydrochloric acid and concentrated to 5 ml. This was acidified to precipitate the acidic fraction (0·441 g., 94%), shown to be largely *N*-benzoyl-DL-asparagine by the m. p. 190—192° (decomp.; after sintering). The whole fraction was dissolved in aqueous sodium hydroxide (3 ml., 1 equiv.) and precipitated fractionally with portions (0·2 ml.) of 1·16N-hydrochloric acid. The first two fractions were combined (73 mg.), m. p. 197—199°, redissolved in aqueous sodium carbonate (1·5 ml., 1 equiv.), and precipitated with hydrochloric acid (0·5 equiv.). Slightly impure *N*-benzoyl-DL-*iso*asparagine separated (24 mg.), m. p. 202—204° raised to 205—207° in admixture with a pure specimen.

The imide (0·1 g.) was also hydrolysed quantitatively by being warmed with 0·28N-sodium carbonate (5 ml., *ca.* 3 equiv.) at 50° for 3 hr. The product (0·11 g.), m. p. 190—191° (decomp.; after sintering), was similar to that above.

Action of Bases on N-*Benzoyl*-DL-*iso*asparagine *Ethyl Ester* (II*a*).—This ester (0·1 g.) was warmed with 0·28N-sodium carbonate (4·2 ml., 3 equiv.) at 40° to give a clear solution after 2 hr. After a further 2 hr., the cooled solution was adjusted to pH 7, extracted with ethyl acetate (3 × 15 ml.), concentrated to 4 ml., and acidified. The product crystallised as needles (85 mg.), m. p. 190—192°, after sintering at 175°. A portion (9·9 mg.) in water (10 ml.) was run on to a column (1 cm. × 15 cm.) of IR-4B resin which had been washed thoroughly with N-hydrochloric acid and distilled water. The column was eluted with N-acetic acid (50 ml.) and then with N-hydrochloric acid (30 ml.). The latter eluted the asparagine derivative (V*a*) (6·4 mg., 65%). Trial experiments with synthetic mixtures of the two amides (V*a*) and (VI*a*) had shown that complete separation was achieved under these conditions, the weaker acid (VI*a*) being eluted by the acetic acid.

A suspension of the ester (II*a*) in 0·11N-sodium hydroxide (1·1 equiv.) was shaken at room temperature for 1 hr. to give a clear solution. This yielded a similar product to that above on being worked up in the same way.

Glycine n-*Hexylamide* (XII; R = H).—*n*-Hexylamine (6·28 g., 2 mol.) in dioxan (30 ml.) was added during 40 min. to a stirred solution of phthaloylglycyl chloride (6 g.) (Sheehan and Frank, *J. Amer. Chem. Soc.*, 1949, **71**, 1856) in dioxan (100 ml.) and chloroform (20 ml.) at 0°. The solution was evaporated to one-third bulk, and aqueous sodium hydrogen carbonate (0·5%, 200 ml.) was added. The precipitated solid, m. p. 163—165°, was washed with water and recrystallised from 50% aqueous ethanol (200 ml.) to give *phthaloylglycine* n-*hexylamide* as long needles (5·7 g., 64%), m. p. 164—166° raised by further recrystallisation from the same solvent to 166—167° (Found: C, 66·5; H, 7·2; N, 10·2. $C_{16}H_{20}O_3N_2$ requires C, 66·6; H, 7·0; N, 9·7%).

A solution of the foregoing product (32·4 g.) in ethanol (700 ml.) was heated under reflux with N-ethanolic hydrazine hydrate (113 ml.) for 1 hr. The cooled solution was filtered and evaporated to dryness. Treatment of the residue with warm N-hydrochloric acid (600 ml.) and removal of the precipitated phthalhydrazide gave a clear solution which was evaporated to a gum. After being thoroughly dried (P_2O_5), the gum crystallised from ethanol–ethyl acetate (1 : 10) to give *glycine* n-*hexylamide hydrochloride* as hygroscopic plates (11·35 g., 52%), m. p. 249° (decomp.; after considerable sintering at 95°) (Found, in material dried at 78°: C, 49·3; H, 10·0%; equiv., 199. $C_8H_{19}ON_2Cl$ requires C, 49·3; H, 9·8%; equiv., 194·5).

*γ-Ethyl Benzyloxycarbonylglycylglycyl-*L-*glutamate* (I*e*).—After many experiments in which the effect of temperature, reaction time, and solvent was studied, the following satisfactory procedure was used. A vigorously stirred solution of benzyloxycarbonylglycylglycine (21·7 g.) (Bergmann and Zervas, *Ber.*, 1932, **65**, 1192) and triethylamine (12 ml.) in chloroform (210 ml.) was treated at 0° with ethyl chloroformate (7·8 ml.). After 25 min., a solution of γ-ethyl

L-glutamate (21·4 g.) (Miller and Waelsch, *loc. cit.*) in 0·1N-sodium hydroxide (118 ml.) was added and stirring was continued for 2 hr. at 0° and 2 hr. at room temperature. After being filtered, the aqueous and the chloroform layer were separated and the latter was washed with aqueous ammonia (1·5%, 2 × 100 ml.) and water (100 ml.). Evaporation of the dried chloroform layer left a neutral gum which was not further examined. All the aqueous solutions were combined and acidified. The precipitated oil rapidly crystallised, and the solid was recrystallised from water (170 ml.) to give the *tripeptide* (I*e*) (8·4 g., 24%), m. p. 144—146°, unchanged by recrystallisation from water (Found: C, 53·9; H, 6·1; N, 10·0%; equiv., 424. $C_{19}H_{25}O_6N_3$ requires C, 53·9; H, 6·0; N, 9·9%; equiv., 423).

The tripeptide (I*e*) (2 g.) was fractionated by counter current distribution (100 transfers) between *sec.*-butanol and aqueous phosphate buffer made from 0·5M-KH_2PO_4 (9 vol.) and 0·5M-K_2HPO_4 (1 vol.). A single peak (K 2·45) was obtained which fitted the theoretical curve (Craig and Craig, *loc. cit.*). The tripeptide, recovered as in previous cases from tubes 64—83, was obtained as needles (1·5 g.), m. p. 151—153°, by crystallisation from water. When chromatographed on Whatman No. 1 paper with *sec.*-butanol (100 vol.) and aqueous ammonia (3%, 40 vol.) as the solvent system, this product had R_F 0·61; benzyloxycarbonylglycylglycine had R_F 0·38 in the same solvent.

Ethoxycarbonylglycine n-*Hexylamide* (XII; R = CO_2Et).—Ethyl chloroformate (0·1 ml.) was added to a solution of glycine *n*-hexylamide hydrochloride (0·2 g.) and triethylamine (0·35 ml.) in warm dioxan (10 ml.). After 0·5 hr. at 50°, the solution was poured into ethyl acetate (100 ml.) and extracted successively with portions (10 ml.) of N-hydrochloric acid, water, saturated aqueous sodium hydrogen carbonate, and finally water. The dried ethyl acetate solution was evaporated, and the residue crystallised from aqueous ethanol as large plates, m. p. 94—95°. A sample of the *amide* was sublimed at 85° (bath)/0·01 mm. for analysis (Found: C, 57·1; H, 9·7; N, 12·5. $C_{11}H_{22}O_3N_2$ requires C, 57·3; H, 9·6; N, 12·2%).

General Method for Preparation of Glycine n-*Hexylamides of Acyl Aspartic and Glutamic Acid Mono-esters.*—A solution of the mono-ester (5 mmol.) in dioxan (80 ml.) and chloroform (15 ml.) was stirred at 0° with triethylamine (0·7 ml.) and ethyl chloroformate (0·48 ml.). After 20 min., a further portion (0·7 ml.) of triethylamine was added, followed immediately by a solution of glycine *n*-hexylamide hydrochloride (5 mmol.) in dioxan (15 ml.) and water (1 ml.). The mixture was stirred for 2 hr. at 0°, then 2 hr. at room temperature, and finally adjusted to pH 6 with hydrochloric acid. Water (50 ml.) was added and the chloroform and dioxan were evaporated. The oil which separated was extracted into ethyl acetate (3 × 100 ml.) and the extract was washed with 2N-hydrochloric acid (10 ml.), saturated aqueous sodium hydrogen carbonate (15 ml.), and finally with water. Evaporation of the dried extract left the coupled product as a gum. Unchanged monoester (*ca.* 25%) was recovered from the alkaline extracts by acidification. The following peptides were prepared by this method:

(a) N-*Benzoyl*-α-DL-*aspartylglycine* n-*hexylamide ethyl ester* (II*b*) crystallised as long needles (80% based on unrecovered monoester), m. p. 99—102° raised by recrystallisation thrice from aqueous ethanol to 105—107° (Found: C, 62·5; H, 7·6; N, 10·4. $C_{21}H_{31}O_5N_3$ requires C, 62·2; H, 7·7; N, 10·4%). The mother-liquor from the first crystallisation of the peptide (II*b*) was concentrated to low bulk, and a solid separated (0·14 g.). This was recrystallised thrice from aqueous ethanol to give large plates, m. p. 93—95° raised to 94—95° in admixture with authentic ethoxycarbonylglycine *n*-hexylamide above.

(b) N-*Benzoyl*-β-DL-*aspartylglycine* n-*hexylamide ethyl ester* (X*b*) (60%) crystallised as fine needles, m. p. 82—87° after sintering (Found, in material dried at 56°: C, 61·9; H, 7·7; N, 10·1. $C_{21}H_{31}O_5N_3$ requires C, 62·2; H, 7·7; N, 10·4%).

(c) N-*Benzoyl*-α-DL-*glutamylglycine* n-*hexylamide ethyl ester* (II*d*) crystallised as felted needles (84%), m. p. 108—109° raised by three recrystallisations from aqueous ethanol to 110—112° (Found: C, 63·1; H, 7·9; N, 10·2. $C_{22}H_{33}O_5N_3$ requires C, 63·0; H, 7·9; N, 10·0%).

(d) N-*Benzyloxycarbonylglycylglycyl*-α-L-*glutamylglycine* n-*hexylamide ethyl ester* (II*e*) was prepared as above save that the mono ester (I*e*) (5 mmole) was dissolved in dioxan (50 ml.) and toluene (35 ml.) to avoid racemisation (Vaughan, *J. Amer. Chem. Soc.*, 1952, **74**, 6137). The peptide crystallised from aqueous ethanol as rosettes of needles (76%), m. p. 142—147°, after sintering, $[\alpha]_D^{18}$ +3·6° (*c*, 4·88 in EtOH) (Found: C, 57·6; H, 7·3; N, 12·2. $C_{27}H_{41}O_8N_5$ requires C, 57·5; H, 7·3; N, 12·4%).

N-*Benzoyl*-α- *and* -β-DL-*aspartylglycine* n-*Hexylamides* (VI*b*) *and* (V*b*).—A solution of glycine *n*-hexylamide hydrochloride (0·72 g.) and triethylamine (1·05 ml., 2 equiv.) in dioxan (35 ml.) and chloroform (10 ml.) was warmed at 40° for 4 hr. with *N*-benzoyl-DL-aspartic anhydride (0·82 g.). The solvents were evaporated with occasional addition of water (total 40 ml.), and

the final aqueous solution was acidified and extracted with ethyl acetate (3 × 70 ml.). After being washed with water, the extract was shaken with an excess of 2N-aqueous ammonia. The alkaline solution was acidified, and the oil which was precipitated gradually crystallised (1·09 g., 77%), m. p. 150—162°. A sample (0·3 g.) was fractionated by countercurrent distribution (40 transfers) between ethyl acetate (8 vol.), *n*-butanol (2 vol.), and aqueous phosphate buffer (11·2 vol.) made from 0·5M-KH_2PO_4 (11 vol.) and 0·5M-K_2HPO_4 (1·6 vol.). Two completely separated peaks were obtained (*K* 1·05, 43%; *K* 5·15, 57%). The aqueous layer from tubes 13—27 (*K* 1·05) was acidified and then shaken with the organic layer from the same tubes, followed by two extractions with ethyl acetate. The combined organic extracts were shaken with an excess of aqueous sodium carbonate solution and the separated aqueous phase was acidified. N-*Benzoyl*-β-DL-*aspartylglycine* n-*hexylamide* (V*b*) separated as needles (88 mg.), m. p. 163—164° (decomp.), unchanged by recrystallisation from water (Found: C, 60·5; H, 7·2; N, 10·9%; equiv., 372. $C_{19}H_{27}O_5N_3$ requires C, 60·5; H, 7·2; N, 11·1%; equiv., 377). N-*Benzoyl*-α-DL-*aspartylglycine* n-*hexylamide* (VI*b*), recovered in the same way from tubes 30—42 (*K* 5·15), formed needles (111 mg.), m. p. 179—180° (decomp.), unchanged by recrystallisation from water (Found: C, 60·3; H, 7·1; N, 10·9%; equiv., 368).

The ester (II*b*) (1 g.) was boiled with acetone (12·5 ml.), water (8·5 ml.), and concentrated hydrochloric acid (3·8 ml.) for 2 hr. and the products were separated into an acidic and a neutral fraction as usual. The former, crystallised from water, gave the weaker acid (VI*b*) (0·384 g., 40%), m. p. 176—176·5° raised to 176·5—177° in admixture with the foregoing sample.

N-*Benzoyl*-DL-*asparaginylglycine* n-*Hexylamide* (XI*b*).—This was prepared from the related acid (VI*b*) on the 1 mmole scale as for the amide (II*a*) save that dioxan (22 ml.) and chloroform (4 ml.) had to be used to obtain a clear solution. The *asparaginyl peptide* (XI*b*) crystallised from aqueous ethanol as fine needles (66%), m. p. 184—185·5° raised to 186—187° by one recrystallisation from the same solvent (Found: C, 60·1; H, 7·6; N, 15·3. $C_{19}H_{28}O_4N_4$ requires C, 60·6; H, 7·5; N, 14·9%).

The ester (II*b*) when treated with saturated alcoholic ammonia solution at room temperature for 4 days gave a neutral fraction from which the asparaginyl peptide (XI*b*) was isolated (12%) by crystallisation from aqueous ethanol. The m. p. 183—184° was unchanged in admixture with the foregoing product.

N-*Acetylglycylglycyl*-α-L-*glutamylglycine* n-*Hexylamide Ethyl Ester* (II*f*).—A solution of the benzyloxycarbonyl tetrapeptide (II*e*) (6 g.) in methanol (250 ml.) containing glacial acetic acid (0·8 ml.) was shaken with hydrogen and palladium oxide (0·4 g.) until the evolution of carbon dioxide ceased. The filtered solution was evaporated to a gum which was treated with water (200 ml.), and the insoluble matter (1·71 g.) was filtered off. The latter crystallised from aqueous ethanol to afford unchanged starting material (1·55 g.), m. p. 138—142° (sintering at 120°), raised to 140—144° (after sintering) in admixture with authentic (II*e*). The aqueous filtrate above was shaken with acetic anhydride (160 ml.) for 20 min. with cooling to keep the temperature below 45°. A second portion (30 ml.) of acetic anhydride was added and, after being shaken for 5 min., the solution was set aside for 3·5 hr. Evaporation left a gum which crystallised from water (70 ml.) to give the *acetyltetrapeptide* (II*f*) (1·2 g.), m. p. 190—194°, after sintering. Treatment of the mother-liquor from this crop with acetic anhydride (60 ml.) as before gave a second crop (0·6 g.) of (II*f*), m. p. 188—195°, and concentration of the final mother-liquor gave a third crop (0·64 g.), m. p. 187—189° (total yield 2·44 g., 65% based on unrecovered starting material). The first crop, recrystallised twice from water gave needles, m. p. 193·5—194·5° (Found: C, 53·9; H, 8·0; N, 15·1. $C_{21}H_{37}O_7N_5$ requires C, 53·5; H, 7·9; N, 14·9%).

Action of Bases on the Esters and Amides of Aspartyl Peptides.—(a) *On* N-*benzoyl*-α-DL-*aspartylglycine* n-*hexylamide ethyl ester* (II*b*). This ester (0·71 g.) was stirred with 0·28N-sodium carbonate (25 ml., 4 equiv.) at 40°. After 2 hr., the undissolved oil was removed, dissolved in ethanol (0·5 ml.), and returned to the reaction mixture. A cloudy solution was obtained which rapidly became clear. After 4 hr., the cooled solution was adjusted to pH 7, freed from neutral matter (12 mg.) by extraction with ethyl acetate, and acidified. The precipitated oil rapidly crystallised (0·63 g., 95%); it had m. p. 155—157° (decomp.; after sintering). A portion (0·3 g.) of this product was fractionated by countercurrent distribution (40 transfers) in the same solvent system as used above for the separation of the acidic aspartyl peptides (V*b*) and (VI*b*). The same two peaks were obtained. From one (*K* 1·05, 75%), the stronger acid (V*b*) was isolated as before, having m. p. 160—162° (decomp.) alone or in admixture with the earlier sample. The other peak (*K* 5·6, 25%) yielded the weaker acid (VI*b*), m. p. 177—179° (decomp.) raised to 178—180° in admixture with the earlier sample.

In a second experiment on the same scale, the material (0·15 g.) undissolved after 2 hr. was collected and washed with water. It crystallised from aqueous ethanol to afford DL-*benzamidosuccinoylglycine* n-*hexylamide* (IV*b*) as stout prisms, m. p. 149—150° (Found: C, 63·1; H, 7·1. $C_{19}H_{28}O_4N_2$ requires C, 63·5; H, 7·0%).

(b) *On* N-*benzoyl*-β-DL-*aspartylglycine* n-*hexylamide ethyl ester* (X*b*). This was treated as above on $\frac{1}{5}$-scale and the material (37 mg.) undissolved after 3·5 hr. was crystallised from aqueous ethanol to give the imide (IV*b*), m. p. 148—149° alone or in admixture with the foregoing product. The mother-liquors from the imide were added to the main alkaline solution, which was then warmed at 50° for a further hour. The acidic products (91 mg.) were isolated as before and fractionated by countercurrent distribution (40 transfers) in the solvent system used in the previous experiment. Two peaks (*K* 1·05, 77%; *K* 5·15, 23%) were obtained corresponding to the isomeric acids (V*b*) and (VI*b*) respectively. It was confirmed that the latter band contained the weaker acid (VI*b*) by isolation of the solute from tubes 29—38 as earlier; m. p. 175·5—176° raised to 176—177° in admixture with an authentic sample.

(c) *On* N-*benzoyl*-DL-*asparginylglycine* n-*hexylamide* (XI*b*). Ammonia was slowly evolved when this peptide (0·1 g.) was shaken vigorously with 0·1N-sodium hydroxide (8 ml., 3 equiv.) at room temperature for 6 hr. Unchanged starting material (82 mg.) was filtered off, and the acidic products (14 mg.), m. p. 143—144·5°, were recovered from the filtrate as before.

A second portion of the peptide (XI*b*) (0·1 g.) was heated for 6 hr. at 50° with 0·25N-sodium carbonate (3·2 ml., 3 equiv.). The products were worked up as before to afford recovered starting material (79 mg.) and an acidic fraction (14 mg.), m. p. 149—151°.

The two portions of acidic material were combined and fractionated by countercurrent distribution (40 transfers) in the solvent system used in the previous experiment. The areas under the two peaks obtained (*K* 1·0 and 5·1) showed that the two components were present approximately in the ratio 3 : 1 respectively. The solute recovered from tubes 15—26 (*K* 1·0) was the stronger acid (V*b*), m. p. 157·5—158° alone or in admixture with an authentic sample.

Action of Bases on the Esters of Glutamyl Peptides.—(a) *On* N-*benzoyl*-α-DL-*glutamylglycine* n-*hexylamide ethyl ester* (II*d*). The peptide (0·419 g.) was stirred with 0·25N-sodium carbonate (16 ml., 4 equiv.) at 50° for 7 hr. Unchanged material (0·269 g.) was filtered off, and the acidic products (0·136 g.), m. p. 123—150°, were recovered from the filtrate as usual.

In a second experiment, the peptide (II*d*) (0·419 g.) was shaken vigorously at room temperature with 0·1N-sodium hydroxide (18 ml., 1·8 equiv.) and after 4 hr. a trace of starting material (5 mg.), m. p. 108—109°, was filtered off. The acidic products (0·361 g., 93%), m. p. 125—155°, were isolated as usual and fractionated by countercurrent distribution (40 transfers) between ethyl acetate (4 vol.), *n*-butanol (1 vol.), and aqueous phosphate buffer (5·6 vol.) made from 0·5M-KH_2PO_4 (4 vol.) and 0·5M-K_2HPO_4 (2·8 vol.). Two separate peaks (*K* 0·45, 57%; *K* 2·8, 43%) were obtained. The solute from the former (tubes 7—19) was recovered as usual and crystallised from 30% aqueous ethanol to give N-*benzoyl*-γ-DL-*glutamylglycine* n-*hexylamide* (V*d*) as needles (135 mg.), m. p. 129—131° (after sintering), unchanged by recrystallisation from the same solvent (Found: C, 61·1; H, 7·4; N, 10·8. $C_{20}H_{29}O_5N_3$ requires C, 61·4; H, 7·5; N, 10·7%).

The solute from the second band (tubes 24—36) was recovered and crystallised in the same way to give N-*benzoyl*-α-DL-*glutamylglycine* n-*hexylamide* (VI*d*) as shining plates (0·107 g.), m. p. 183—185°, raised to 184—186° by one recrystallisation from 30% aqueous ethanol (Found: C, 61·6; H, 7·4; N, 10·3%).

The ester (II*d*) was treated at room temperature in ethanol with N-sodium hydroxide (0·3 equiv.) for 4 days, and in a second experiment with sodium ethoxide (1 equiv.) for 1 week, but in neither case could the imide (IV*d*) be isolated from the neutral products.

(b) *On* N-*acetylglycylglycylglycyl*-α-L-*glutamylglycine* n-*hexylamide ethyl ester* (II*f*). This ester (2·31 g.) was shaken with 0·1N-sodium hydroxide (62 ml., 1·2 equiv.), and after 6 hr. at room temperature, the clear solution was extracted with ethyl acetate (2 × 50 ml.). The aqueous layer was adjusted to pH 5, concentrated to 15 ml., and acidified. N-*Acetylglycylglycylglycyl*-γ-DL-*glutamylglycine* n-*hexylamide* (V*f*) separated as plates (1·22 g., 56%), m. p. 186—190° raised to 194·5—195·5° by recrystallisation from water, $[\alpha]_D^{18}$ 0° ± 0·1° (*c*, 12·4 in 1·2 equiv. of aqueous NaOH) (Found: C, 51·5; H, 7·4; N, 15·6%; equiv., 439. $C_{19}H_{33}O_7N_5$ requires C, 51·5; H, 7·5; N, 15·8%; equiv., 443); it had pK_a, 3·45 by potentiometric titration in water.

The mother-liquor from (V*f*) was concentrated to yield a second crop of acidic matter 0·508 g.), m. p. 185—187° (after sintering), and the final mother-liquor was evaporated to a gum. The latter was worked through dimethylformamide, ethanol, and ethyl acetate to remove inorganic salt, and finally obtained as an amorphous solid (182 mg.) which contained an

appreciable amount of chloride ion but no sodium ion. The second crop above, recrystallised from water, gave needles (293 mg.) (Found: equiv., 446), m. p. 194—195·5° depressed in admixture with (V*f*). A portion of this material was completely hydrolysed by being heated with 6N-hydrochloric acid for 20 hr. at 110°. The presence in the hydrolysate of glutamic acid, glycine, and *n*-hexylamine was shown by paper chromatography.

N-*Benzoyl*-DL-*glutamic Anhydride* (VII*c*).—Anhydrous *N*-benzoyl-DL-glutamic acid (13 g.) (Fischer, *Ber.*, 1899, **32**, 2464) was heated at 100° with acetic anhydride (40 ml.) until a clear solution resulted and then for a further 10 min. The solution was cooled to 0°, and the *anhydride* (10·5 g., 87%) collected and washed with anhydrous light petroleum. Recrystallised from acetic anhydride, it formed large plates, m. p. 154—155° (Found: C, 62·2; H, 4·9; N, 6·0. $C_{12}H_{11}O_4N$ requires C, 61·8; H, 4·8; N, 6·0%).

N-*Benzoyl- and -α-γ-*DL-*glutamylglycine n-Hexylamides* (VI*d*) *and* (V*d*).—These were prepared from glycine *n*-hexylamide hydrochloride (0·98 g.) and benzoylglutamic anhydride (1·17 g.) in the way used above for the aspartyl analogues. During the isolation of the acidic products as before, a portion (0·45 g.) failed to dissolve in ethyl acetate and was shown to be the pure weak acid (VI*d*) by its m. p. 184—186° alone or in admixture with the sample above. The remaining acidic material in the ethyl acetate was shaken with 0·25N-sodium carbonate (3 × 10 ml.) and finally with an excess of 2N-aqueous ammonia. The second and the third carbonate extract were combined and acidified. The precipitated solid (42 mg.) was recrystallised from 30% aqueous ethanol to afford the stronger acid (V*d*), m. p. 127—129° raised to 128—130° in admixture with the pure sample obtained as above. The ammoniacal solution, when acidified, precipitated a mixture of the two acids (V*d*) and (VI*d*) (1·25 g.), m. p. 125—170° (total yield of acidic material 87%).

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The Composition of Acacia cyanophylla *Gum.*

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Acacia cyanophylla gum on hydrolysis gives L-rhamnose (5 mols.), L-arabinose (2 mols.), D-galactose (11 mols.), and D-glucuronic acid (5 mols.), and its equivalent weight is therefore unusually low in comparison with those of other gums from *Acacia* species. The acid residues are recovered as 6-*O*-β-D-glucuronosyl-D-galactose on autohydrolysis of the gum acid and on partial hydrolysis of the resulting degraded polysaccharide. The disaccharide 3-*O*-α-D-galactopyranosyl-L-arabinose occurs in the products of autohydrolysis. The structure of the gum must therefore differ considerably from that exuded by *A. pycnantha* (Hirst and Perlin, *J.*, 1954, 2622), a species very closely related botanically to *A. cyanophylla*.

DESPITE the widespread use of a general term " gum arabic " to denote the polysaccharide gums from such diverse sources as *A. senegal*, *A. verek*, and others (Pigman and Goepp, " Chemistry of the Carbohydrates," Academic Press, New York, 1948, p. 631; Whistler and Smart, " Polysaccharide Chemistry," Academic Press, New York, 1953, p. 304), it has become apparent that considerable variation is to be expected in the structure of gums isolated from different *Acacia* species. *A. mollissima* gum, for example, contains the same monosaccharide and uronic acid components but has an equivalent weight greater than the average value found for gums hitherto classed as gum arabic (Stephen,

J., 1951, 646), while a very recent paper by Hirst and Perlin (*J.*, 1954, 2622) has shown the equivalent weight of *A. pycnantha* gum to be even higher. As part of a programme to elaborate further the variation of gum composition with species of *Acacia*, the gums of *A. cyanophylla* and *A. karroo* have been examined by us during the past two years, and the first part of this work is now reported. A fair-sized, leafy tree, *A. cyanophylla* Lindl. (Port Jackson willow; golden willow) was introduced from Australia into the winter-rainfall region of the Cape Province in the middle of the 19th century, and has flourished in sandy coastal areas; it has proved to be a comparatively poor source of gum. *A. pycnantha* Benth. is closely related botanically to *A. cyanophylla* but is rare in the Western Cape; we intend to collect gum from this species for comparison with the material of South Australian origin described by Hirst and Perlin (*loc. cit.*).

Purified *A. cyanophylla* gum acid has a negative specific rotation, in common with those of the other *Acacia* gums hitherto examined, but the equivalent weight (740) is considerably lower. No significant differences have been detected between samples obtained from trees grown within a radius of several miles, and a preparation investigated electrophoretically showed single boundaries on both the ascending and the descending side. Although the descending boundaries exhibited considerable spreading, the ascending boundaries were very sharp. No further proof of homogeneity can be put forward. Commercial "gum arabic," procured from Eimer and Amend Co., New York, moves at a very different rate from cyanophylla gum acid (Joubert, *J. S. African Chem. Inst.*, in the press).

Paper-chromatographic examination of the hydrolysis of the gum acid in water at 95° showed the liberation within 4 hours of rhamnose, arabinose, and a disaccharide, followed, after 23 hours, by galactose and an aldobiuronic acid. The sugars were identified as L-rhamnose, L-arabinose, and D-galactose by chromatographic separation (Hough, Jones, and Wadman, *J.*, 1949, 2511), and the preparation of crystalline derivatives. The disaccharide formed an osazone whose m. p. corresponded with that obtained for 3-*O*-α-D-galactopyranosyl-L-arabinose phenylosazone by Jones (*J.*, 1953, 1672), and on methylation gave a crystalline heptamethyl derivative whose physical constants agree with those given by Smith (*J.*, 1939, 744) for the methylated disaccharide; it has not been isolated from *A. pycnantha* gum. These workers obtained their material from "gum arabic, Turc. variety" and "gum kordofan" respectively. The aldobiuronic acid liberated on autohydrolysis was 6-*O*-β-D-glucuronosyl-D-galactose, the same product as has been isolated from *A. mollissima* and *A. pycnantha* gums. It was homogeneous according to prolonged paper chromatography in an acid–ethyl acetate mixture, and formed a crystalline hepta-*O*-methyl methyl ester (cf. Challinor, Haworth, and Hirst, *J.*, 1931, 258).

The polysaccharide remaining after hydrolysis in water for 75 hours had almost the same equivalent weight (700) as the original gum acid, the splitting off of sugar residues being compensated by the liberation of aldobiuronic acid. Hydrolysis of this polysaccharide with dilute sulphuric acid gave D-galactose and an aldobiuronic acid identical with that produced during autohydrolysis.

Assay by the method of Hirst and Jones (*J.*, 1949, 1659) of the sugars produced on prolonged acid hydrolysis of the gum showed that L-rhamnose (5), L-arabinose (2), D-galactose (11), and D-glucuronic acid (5 mols.) must be linked together in the gum in the proportions indicated. The low proportion of arabinose necessitates the postulation of a repeating unit containing not 1 but at least 5 acid residues, in much the same way as the low rhamnose content of *A. pycnantha* gum (Hirst and Perlin, *loc. cit.*) requires 4 acid residues per repeating unit.

The composition of the gum from *A. cyanophylla* is therefore markedly different from that of *A. pycnantha* despite a close botanical connection and the identity of the ultimate hydrolysis products of the two gums. The rhamnose and uronic acid contents of *A. cyanophylla* gum are unusually high, but the ratio of these two residues is very nearly unity, as for the gums from *A. senegal* (Butler and Cretcher, *J. Amer. Chem. Soc.*, 1929, **51**, 1519) and *A. mollissima*. This may mean that rhamnose is linked glycosidically to the acid residues in these gums (cf. Charlson, Ph.D. thesis, Cape Town, 1954).

Experimental

Unless otherwise stated, concentration of solutions was carried out at 40°/20 mm., and specific rotations were measured in aqueous solution. Paper chromatograms were run at 27° in butanol–ethanol–water (20 : 1 : 3), ethyl acetate–acetic acid–formic acid–water (18 : 3 : 1 : 4) (Jones, *loc. cit.*), or butanol–pyridine–water (9 : 2 : 2).

Purification of A. cyanophylla *Gum.*—The bulk of the gum was collected during autumn from a small plantation near Retreat in the Western Province of the Cape; the trees were identified by courtesy of the Bolus Herbarium. No attempt was made to separate the clear transparent jelly-like material from dried-out resinous lumps.

Crude gum (100 g.) was purified in the standard manner (Smith, *J.*, 1939, 744) by precipitation in ethanol from dilute hydrochloric acid and then aqueous solution (four times in all) and after drying at 45° in partial vacuum for 30 hr. was a white amorphous powder (65 g.), $[\alpha]_D^{16}$ −20° (*c*, 0·68) [Found: Loss at 100°/20 mm., 10·4; sulphated ash, 0·73; N, 0·17%; equiv., 740 (on dry basis); iodine absorption, 2·1 c.c. of 0·1N-iodine per g. after 20 minutes' oxidation]. Samples from different trees and different plantations had almost identical specific rotations and equivalent weights.

Hydrolyses of the Gum.—(a) *Total hydrolysis.* The purified gum acid was completely hydrolysed by 2N-sulphuric acid at 100° for 14 hr., as shown by filter paper chromatography of the neutralised hydrolysate (Partridge, *Nature*, 1946, **158**, 270; Flood, Hirst, and Jones, *J.*, 1948, 1679). Quantitative analysis (Hirst and Jones, *loc. cit.*) indicated that the products were galactose, arabinose, and rhamnose in the approximate molar ratio of 11·1 : 2 : 5 (mean of six determinations).

(b) *Partial hydrolysis.* The progress of hydrolysis of the gum acid (54 g.) in water (1 l.) at 90—95° was followed by polarimetric and iodometric observations: $[\alpha]_D$ −20° (initial), +18° (14 hr.), +23° (20 hr.), +25° (24 hr.), +27° (32 hr.), +28° (38 hr.), *ca.* +30° (50 hr.). Iodine values expressed as c.c. of 0·1N-iodine per g.: 2·3 (initial), 15·7 (4 hr.), 24·0 (8 hr.), 29·4 (12 hr.), 38·6 (20 hr.), 47·0 (32 hr.), 50·1 (38 hr.), 55·6 (50 hr.), 62·5 (66 hr.), 63·2 (75 hr.). Examination on a paper chromatogram after 4 hr. showed rhamnose, arabinose, and a disaccharide, which later increased slowly in amount; galactose and an aldobiuronic acid were found after 23 hr. The cooled, filtered solution was concentrated to 400 c.c. and poured into ethanol (1·5 l.), whereupon a degraded acid (C), $[\alpha]_D$ *ca.* 0° (*c*, 0·58), was precipitated (27·3 g., dried at 45° *in vacuo*) [Found: Loss at 100°/20 mm., 6·7%; equiv., 700 (on dry basis)]. Concentration of the neutralised (barium carbonate) filtrate (to 80 c.c.) followed by pouring into methanol (1 l.) afforded a slimy precipitate of barium salts (B; 8·3 g.), and, from the filtrate, a syrupy mixture of reducing sugars (A; 17·5 g.)

Examination of the Sugars (A).—Paper chromatography disclosed rhamnose, arabinose, galactose, a disaccharide, and a small amount of mixed barium salts at the origin. The syrup (0·2 g.) was then heated with 2N-sulphuric acid (5 c.c.) in a sealed tube at 100° for 14 hr. and analysed (Hirst and Jones, *loc. cit.*): rhamnose, arabinose, and galactose were found in the molar ratio 5·0 : 1·9 : 1·2.

Trituration of syrup (A) (16·5 g.) with cold methanol and storage in the ice-chest gave crystals (5 g.) which after separation on a porous tile and recrystallisation from ethanol proved to be α-L-rhamnose hydrate, m. p. and mixed m. p. 93—94°, $[\alpha]_D^{16}$ +9° (*c*, 2·1) [phenylosazone m. p. and mixed m. p. 175° (decomp.)]. Half of the residual syrup (5·1 g.) was separated by elution from a cellulose column (Hough, Jones, and Wadman, *loc. cit.*) with half-saturated aqueous butanol, α-L-rhamnose (1·9 g.), L-arabinose (1·2 g.), and D-galactose (0·6 g.) being obtained crystalline. The arabinose was identified through its m. p. and mixed m. p., 156°, $[\alpha]_D^{20}$ +105° (*c*, 1·0), and formation of its benzoylhydrazone, m. p. and mixed m. p. 204° (from ethanol); the galactose had m. p. and mixed m. p. 164°, $[\alpha]_D^{18}$ +79° (*c*, 1·2), and gave mucic acid on oxidation. Further elution, with 96% aqueous ethanol, afforded a chromatographically pure reducing disaccharide (0·6 g.), $[\alpha]_D^{16}$ +152° (*c*, 2·3), R_{gal} (relative to galactose) 0·50 in the basic solvent mixture; it consisted of galactose and arabinose which were detected on a paper chromatogram after hydrolysis of a small portion with 0·5N-sulphuric acid. The rate of movement of this disaccharide was identical with that of the chief disaccharide component of autohydrolysed commercial "gum arabic" acid. A mixture of barium salts (0·5 g.) was finally washed from the column with water.

Examination of the Barium Salts (B).—The mixed salts (B) constituted a white amorphous powder which reduced Fehling's solution strongly and had $[\alpha]_D^{17}$ +4° (*c*, 0·46) (Found: Ba,

13·8; iodine absorption, 38 c.c of 0·1N-iodine per g. Calc. for $C_{12}H_{19}O_{12}Ba_{0·5}$: Ba, 16·2%; iodine absorption 47 c.c.). On a descending paper chromatogram run in the acid solvent the main component had R_{gal} 0·27, but there were present also a uronic acid spot, R_{gal} 1·05, and two faint spots between R_{gal} 0·10 and the origin. After hydrolysis of the salts (B) (0·1 g.) with 2N-sulphuric acid (5 c.c.) in a sealed tube at 100° for 14 hr., the neutralised (barium carbonate) product was examined on a paper chromatogram; galactose and a uronic acid were present. Galactose was estimated by adding ribose (53·7 mg.) to a hydrolysate (258 mg.) prepared in this way, and determining the galactose–ribose ratio (Found: galactose, 40·0. Calc. for $C_{12}H_{19}O_{12}Ba_{0·5}$; galactose, 42·5%).

Further Hydrolysis of the Acid (*C*).—The polysaccharide (C) (13 g.) was heated with 0·5N-sulphuric acid (200 c.c.) on a boiling-water bath for 15 hr., during which the iodine absorption rose from 11 c.c. to 86 c.c. and $[\alpha]_D$ from +3° to +35°, with the customary levelling off of these values with time. The neutralised (barium carbonate) hydrolysate was then concentrated (to 50 c.c.) and poured into excess of methanol, whereupon a white amorphous precipitate of barium salts (D) (9 g.), $[\alpha]_D^{17}$ +13° (*c*, 0·7), was formed (Found: Ba, 16·2%; iodine absorption, 57 c.c. of 0·1N-iodine per g.). A slow-moving aldobiuronic acid (R_{gal} 0·27) together with traces of galactose and an uronic acid were present according to a paper chromatogram. (Complete hydrolysis gave a uronic acid and galactose only.) Concentration of the aqueous-methanolic mother-liquors yielded crude D-galactose (5·9 g.), which was purified by one recrystallisation from absolute ethanol and identified in the usual way.

Identification of the Disaccharide Isolated from the Sugars (*A*).—A portion of this disaccharide (0·1 g.) was oxidised with bromine water and barium benzoate (Hudson and Isbell, *Bur. Stand. J. Res.*, 1929, **3**, 58), and after hydrolysis of the product with dilute sulphuric acid the solution was neutralised using Amberlite IR-4B resin. The solution contained galactose (paper chromatogram); arabinose was therefore the aglycone in the disaccharide. On treatment with aqueous phenylhydrazine acetate at 100° for 30 min. the disaccharide formed a pale-yellow phenylosazone which, crystallised from ethanol, had m. p. 235° (decomp.) (Found: C, 55·9; H, 6·3; N, 12·0. Calc. for $C_{23}H_{30}O_8N_4$: C, 56·4; H, 6·1; N, 11·4%); Jones (*loc. cit.*) gives m. p. 240°.

Methylation of the disaccharide (1 g.) in the usual way afforded its crystalline heptamethyl derivative, m. p. 87—88° [from light petroleum (b. p. 40—60°)], $[\alpha]_D^{16}$ +168° (*c*, 1·2) (Found: C, 52·5; H, 8·3; OMe, 52·8. Calc. for $C_{18}H_{34}O_{10}$: C, 52·7; H, 8·4; 7OMe, 52·9%). Smith (*loc. cit.*) reported m. p. 82° and $[\alpha]_D^{18}$ +162° for hepta-*O*-methyl-3-*O*-α-D-galactopyranosyl-L-arabinose. On hydrolysis with dilute sulphuric acid the methylated substance (0·52 g.) gave a syrup (0·48 g.) which showed two large spots R_{MG} 1·0 (relative to tetramethylgalactose) and R_{MG} 0·78, and a much smaller spot R_{MG} 0·60 on a paper chromatogram (basic solvent). By use of butanol containing light petroleum (b. p. 100—120°) as mobile phase the mixture was separated on a cellulose column into (i) a pale yellow syrup (0·21 g.), R_{MG} 1·0, which afforded *N*-phenyl-D-galactosylamine 2 : 3 : 4 : 6-tetramethyl ether, m. p. and mixed m. p. 192°, on treatment with aniline in ethanol, (ii) a mixture (0·13 g.) of the methylated sugars, and (iii) a di-*O*-methylarabinose (0·09 g.), R_{MG} 0·78. Fraction (iii) had $[\alpha]_D^{16}$ +135° (*c*, 1·1) and did not evolve formaldehyde on periodate oxidation, but formed a crystalline derivative, m. p. 137°, on treatment with aniline in ethanol (Found: OMe, 24·6. Calc. for $C_{13}H_{19}O_4N$: 2OMe, 24·6%). These constants are consistent with this derivative's being the aniline compound of 2 : 4-di-*O*-methyl-L-arabinose (lit., m. p. 126°, 142°, 145—146°; aniline derivative of the 2 : 3-dimethyl ether, m. p. 139°). 2 : 3-Di-*O*-methyl-L-arabinose has $[\alpha]_D$ +107°, but should evolve 1 mol. of formaldehyde on periodate oxidation. The recorded $[\alpha]_D$ of the 2 : 4-isomer is +129°, and it should not evolve formaldehyde on periodate oxidation.

Identification of the Uronic Acid.—Barium aldobiuronate (11·5 g.), obtained by the hydrolysis of *A. cyanophylla* gum acid (30 g.) with 0·5N-sulphuric acid for 18 hr., was heated with 2N-sulphuric acid (120 c.c.) in a sealed bottle at 100° for 16 hr. The neutralised (barium carbonate) solution was poured into methanol (1 l.), and the precipitated barium salt was purified by elution from a cellulose column with water, after washing through traces of galactose with propan-2-ol (yield, 3·6 g.) (Found: Ba, 26·0. Calc. for $C_6H_9O_7Ba_{0·5}$: Ba, 26·3%). Barium was removed from an aqueous solution with Amberlite IR-100H resin; the resulting acid solution was then concentrated to a syrup, placed on a cellulose column, and fractionated with half-saturated aqueous butanol as eluant. D-Glucurone, m. p. 179° (lit., m. p. 175—176°), and D-glucuronic acid, m. p. 154°, $[\alpha]_D^{17}$ +33° (*c*, 2·0) (lit., m. p. 156°, $[\alpha]_D^{23}$ +35°), were thereby isolated. The uronic acid was characterised by oxidation with dinitrogen tetroxide in chloroform and condensation of the product with *o*-phenylenediamine to give the dibenziminazole

derivative of D-glucosaccharic acid, m. p. and mixed m. p. 234° (decomp.) (Lohmar, Dimber, Moore, and Link, *J. Biol. Chem.*, **1942**, **143**, 551).

Identification of the Aldobiuronic Acid in Fraction (*D*).—Aldobiuronic acid was obtained from barium salts (D) (4 g.) by de-ionising them with Amberlite IR-100H resin and chromatography on cellulose, wet butanol being used to elute galactose and uronic acid, and 90% aqueous ethanol to elute the aldobiuronic acid (2 g.); this was a stable white solid, $[\alpha]_D^{16}$ −3° (*c*, 2·0), R_{gal} 0·27 (acid solvent) (Found: equiv., 380. Calc. for $C_{12}H_{20}O_{12}$: equiv., 356). The acid (1·3 g.) was methylated in the usual way to give a viscid syrup (1·0 g.), n_D^{20} 1·464, which slowly crystallised. Recrystallisation from light petroleum gave needles, m. p. 86—87°, $[\alpha]_D^{18}$ −35° (*c*, 1·2 in $CHCl_3$) (Found: C, 50·8; H, 7·7; OMe, 53·0. Calc. for $C_{20}H_{36}O_{12}$: C, 51·3; H, 7·8; 8OMe, 53·0%), constants which agree with those reported by Challinor, Haworth, and Hirst (*loc. cit.*) for the methyl ester of methyl hexa-*O*-methyl-6-*O*-β-D-glucuronosyl-β-D-galactoside.

Hydrolysis of this methyl ester (cf. Brown, Hirst, and Jones, *J.*, 1948, 1677) gave an ether-soluble syrup, from which a tri-*O*-methylgalactose (0·14 g.) was isolated on a large paper chromatogram. This methylated sugar had $[\alpha]_D^{20}$ +100° (*c*, 0·9) and R_{MG} 0·87, and gave a crystalline *N*-phenyl-D-galactosylamine trimethyl ether, m. p. 161—162° (lit. m. p. of the 2 : 3 : 4-ether 164—165° to 170°) after recrystallisation from ethanol (Found: OMe, 31·3. Calc. for $C_{15}H_{23}O_5N$: 3OMe, 31·3%); this depressed the m. p. of *N*-phenyl-D-galactosylamine 2 : 4 : 6-trimethyl ether from 169° to 157°. The sugar ether was proved to be 2 : 3 : 4-tri-*O*-methyl-D-galactose by oxidation of a portion (15 mg.) with sodium periodate, whereupon formaldehyde (dimedone compound, m. p. and mixed m. p. 188°; yield 12 mg.) was evolved. The original aldobiuronic acid was therefore 6-*O*-β-D-glucuronosyl-D-galactose.

Identification of Aldobiuronic Acid in Fraction (*B*).—Barium was removed from the salts (B) by treatment with Amberlite IR-100H, and the acidic syrup obtained therefrom was fractionated on cellulose (cf. previous section) to yield an aldobiuronic acid (2 g.), R_{gal} 0·27 in the acid solvent. Complete methylation of this afforded a crystalline derivative, m. p. 86°, $[\alpha]_D^{17}$ −30° (*c*, 1·2 in $CHCl_3$); there was no depression of m. p. on admixture with the hepta-*O*-methyl methyl ester of 6-*O*-β-glucuronosyl-D-galactose described above.

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NOTES.

Reactions between Hydrogen Peroxide and Halide Ions.

By M. C. R. Symons.

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Two fundamentally different mechanisms have been proposed recently for the reactions between hydrogen peroxide and halide ions, both mechanisms being satisfactorily in accord with the observed kinetics (see Morgan, *Quart. Reviews*, 1954, **8**, 123, for references) and with the concepts of reaction mechanisms enumerated by Hinshelwood (*J.*, 1947, 694). Weiss (*Ann. Reports*, 1947, **44**, 60) has proposed a radical mechanism with a first stage similar to that of the reaction between hydrogen peroxide and ferrous ion:

$$\left\{\begin{array}{l} I^- + H_2O_2 \longrightarrow I\cdot + OH^- + \cdot OH \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1) \\ I^- + H_3O_2^+ \longrightarrow I\cdot + H_2O + \cdot OH \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2) \end{array}\right.$$

$$\cdot OH + I^- \longrightarrow OH^- + I\cdot \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

$$2I\cdot \longrightarrow I_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

Reactions (1) and (2) are thought to be rate-determining, thus giving $-d[I^-]/dt = k_1[H_2O_2][I^-] + k_2[H_2O_2][I^-][H^+]$, concordant with experiment. Weiss does not discuss mechanisms for the similar reactions which occur with bromide and chloride ions, but suggests the following mechanism for the reaction between hydrogen peroxide and iodine in less acidic solution and hence, by a combination of the two schemes, a system for the catalytic decomposition of hydrogen peroxide by iodide :

$$I_2 \rightleftharpoons I^+ + I^- \quad . . . . . \quad (5)$$
$$HO_2^- + I^+ \longrightarrow HO_2^{\cdot} + I^{\cdot} \quad . . . . . \quad (6)$$
$$H_2O_2 + HO_2^{\cdot} \longrightarrow O_2 + H_2O + {}^{\cdot}OH \quad . . . . . \quad (7)$$

Hence, Weiss shows that in the stationary state,

$$d[O_2]_2/dt = (k_5k_6[I_2][HO_2^-])/(k_{-5}[I^-] + k_6[HO_2^-])$$

Abel (*Z. physikal. Chem.*, 1928, **136**, 161) has found

$$\frac{d[O_2]}{dt} = \frac{k[I_2][H_2O_2]}{[I^-][H^+]} + \frac{k'[I_2][H_2O_2]}{[I^-][H^+]^2}$$

and Morgan (*loc. cit.*), who strongly supports Weiss's mechanism, shows that if $k_{-5}[I^-] \gg k_6[HO_2^-]$, the derived expression becomes equivalent to the first experimental term. He suggests that the second term shows that reaction (7) must involve O_2^- as well as HO_2; however, it is difficult to see how this could affect the kinetics if reaction (6) is rate-determining.

In an important series of articles, Edwards (*Chem. Reviews*, 1952, **50**, 455; *J. Phys. Chem.*, 1952, **56**, 279; *J. Chem. Educ.*, 1954, **31**, 270; *J. Amer. Chem. Soc.*, 1954, **76**, 1540) has succeeded in correlating a large amount of kinetic data concerning nucleophilic displacement reactions, and has shown that the reactions between hydrogen peroxide and halide ions can be included in this scheme. This correlation provides good circumstantial evidence that these reactions are nucleophilic displacements of the type

$$\left\{\begin{array}{l} X^- + H_2O_2 \longrightarrow XOH + OH^- \quad . . . . . \quad (8) \\ X^- + H_3O_2^+ \longrightarrow XOH + H_2O \quad . . . . . \quad (9) \end{array}\right.$$
$$X^- + XOH \rightleftharpoons X_2 + OH^- \quad . . . . . \quad (10)$$

Edwards does not discuss the reaction between hydrogen peroxide and iodine, but this reaction may be represented in a similar manner :

$$HO_2^- + I_2 \rightleftharpoons HO{\cdot}OI + I^- \quad . . . . . \quad (11)$$
$$HO{\cdot}OI \longrightarrow H^+ + O_2 + I^- \quad . . . . . \quad (12)$$
$$OH^- + HO{\cdot}OI \longrightarrow H_2O + O_2 + I^- \quad . . . . . \quad (13)$$
$$HO_2^- + IOH \longrightarrow O_2 + H_2O + I^- \quad . . . . . \quad (14)$$

Reactions (8) and (9) will be irreversible since XOH would preferentially form XO^- : reaction (10) may proceed *via* XOH_2^+ ; reaction (11) is postulated as a reversible process ; reactions (12) and (13) represent two possible modes for the decomposition of " periodous acid " (HO·OI), and the sequence (8)—(14) represents the simplest mechanism for the catalytic formation of oxygen.

If reactions (8) and (9) are rate-determining, the observed kinetic expression for iodine formation is satisfactorily explained, and if reaction (8) is still rate-determining for the catalytic evolution of oxygen in neutral solution, then $d[O_2]/dt = 2d[I_2]/dt$, as observed experimentally by Brode (*Z. physikal. Chem.*, 1904, **49**, 208). Application of stationary-state kinetics to the sequence (11), (12), (13), treating HO·OI as an unstable intermediate, gives :

$$\frac{d[O_2]}{dt} = \frac{k_{11}k_{12}[HO_2^-][I_2]}{k_{-11}[I^-] + k_{12}} + \frac{k_{11}k_{13}[HO_2^-][I_2][OH^-]}{k_{-11}[I^-] + k_{13}[OH^-]}$$

Provided that $k_{-11}[I^-] \gg k_{12}$ and $k_{-11}[I^-] \gg k_{13}[OH^-]$, this expression approximates to that found experimentally (Abel, *loc. cit.*).

Clearly, both mechanisms require that the evolved oxygen be derived entirely from the hydrogen peroxide, as is found experimentally (Cahill and Taube, *J. Amer. Chem. Soc.*, 1952, **74**, 2312).

Liebhafsky and Mohammed (*ibid.*, 1933, **55**, 3977) have derived a value of 13,400 cal. for the activation energy of the reaction between hydrogen peroxide and iodide, not catalysed by hydrogen ion. By assuming that the heats of solution of hydroxyl radicals and iodine atoms are similar to the corresponding values for water and molecular iodine respectively (cf. Evans, Hush, and Uri, *Quart. Reviews*, 1952, **6**, 188), the change in heat content for reaction (1) is found to be approximately +19,000 cal. (Latimer, "Oxidation Potentials," Prentice-Hall, Inc., New York, 1952), and for reaction (8), when X^- is iodide, to be approximately −24,000 cal. Thus, since the energies of activation of endothermic steps must be equal to, or greater than, their thermochemical heats of reaction, step (1) appears unlikely, but the experimental figures may well describe the transition state $(X \cdots O \cdots \overset{\delta-}{H} \cdots \overset{\delta-}{O}H)$ for step (8).

The intermediates postulated by Weiss, if present, should give rise to certain characteristic induced reactions, and failure of the hydrogen peroxide–iodide system to induce these reactions may be taken as evidence against their presence. Since iodine atoms are known to induce a rapid chain reaction between iodine and oxalate, Taube (*J. Amer. Chem. Soc.*, 1942, **64**, 161) has tested for their presence by adding oxalate to the hydrogen peroxide–iodide–iodine system, and has concluded that they cannot be formed during the reaction. Alternatively, hydroxyl radicals, if present during the reaction, should, in the presence of vinyl monomers, initiate polymerisation (Baxendale, Evans, and Park, *Trans. Faraday Soc.*, 1946, **42**, 155) and, in the presence of benzoic acid, give hydroxylation of the aromatic ring (Bates, Evans, and Uri, *Nature*, 1950, **166**, 869). Extensive tests have been carried out with acrylonitrile, using Thunberg tubes, as described by Drummond and Waters (*J.*, 1953, 2836). The pH was varied by the addition of dilute perchloric acid, and the initial concentration of hydrogen peroxide and sodium halide (chloride, bromide, or iodide) was altered over a wide range in many different experiments, since too high a concentration of radicals may invalidate the test (Dainton, *J.*, 1952, 153). In no instance was polymerisation observed; as a check on the method, it was ascertained that, under similar conditions, the hydrogen peroxide–ferrous sulphate reaction gave instantaneous precipitation of polymer.

Iodide ions should compete with acrylonitrile for hydroxyl radicals, since reaction (3) is strongly exothermic (Evans, Hush, and Uri, *loc. cit.*), but this would be unlikely to suppress polymerisation completely as this is a chain reaction and all experiments were performed with acrylonitrile in large excess. However, a qualitative check on the relative importance of the two competing reactions was devised whereby hydrogen peroxide was added to an acidified, saturated, aqueous solution of acrylonitrile containing iodide ion and a trace of ferrous ion. With small concentrations of iodide, only polymer was formed; with a large excess of iodide only iodine appeared; with intermediate concentrations of iodide both iodine and polymer were produced. Accordingly, it is concluded that when the concentration of acrylonitrile is very much greater than the concentration of iodide, hydroxyl radicals, if present, should give rise to observable polymerisation. A similar exchange occurring during the reaction between hydrogen peroxide and chloride ions would not inhibit polymerisation appreciably, since chlorine atoms are also efficient initiators.

As a further test for the presence of free hydroxide radicals, benzoic acid was treated as above at various temperatures and for various times, but insufficient salicylic acid was formed to give an observable colour with added ferric ion; again, addition of hydrogen peroxide to a solution of benzoic acid containing a trace of ferrous ion gave an immediate purple colour.

It is therefore concluded that free hydroxyl radicals are not formed during these reactions and it is considered that this negative evidence lends further support to the nucleophilic displacement mechanisms proposed by Edwards. These mechanisms are essentially similar to those originally proposed (*e.g.*, by Abel, and by Liebhafsky and

Mohammed, *locc. cit.*) except in so far as they stress the postulated S_N2 nature of the separate steps. In the absence of compelling evidence in favour of the prior hydrolysis of iodine in its reaction with hydrogen peroxide (see, however, Liebhafsky, *Chem. Reviews*, 1935, **17**, 89) the sequence (11)—(13) is considered preferable since it is simpler and seems to be more self-consistent.

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Infra-red Absorption Characteristic of Diazonium Cations.

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IN connection with other work we desired to know whether the infra-red spectra of diazonium salts display any features which could usefully serve for the recognition of the $(R{\cdot}N_2)^+$ cation. As the literature appeared to contain no data on the point we have examined 21 substances which (apart from the zwitter-ionic *p*-diazobenzenesulphonic acid) are either diazonium salts with single anions or complex salts containing diazonium cations. The majority were easily prepared by addition of the appropriate metal halide dissolved in hydrochloric acid to a solution containing the requisite diazonium chloride (for references, see Saunders, "The Aromatic Diazo-compounds and their Technical Applications," E. Arnold and Co., 2nd Edn., London, 1949, pp. 74 *et seq.*). Borofluorides or tetrachloroiodites ($R{\cdot}ICl_4$) were obtained by the procedures described respectively by Le Fèvre and Turner (*J.*, 1930, 1158) and Chattaway, Garton, and Parkes (*J.*, 1924, **125**, 1980). Spectra have been recorded for Nujol mulls with a Perkin–Elmer model 12C spectrometer. In every case a strong absorption band has appeared in the region 2230—2310 cm.$^{-1}$ (see Table).

Diazonium salt	Strong absorption (cm.$^{-1}$)	Diazonium salt	Strong absorption (cm.$^{-1}$)
Benzenediazonium ferrichloride	2256	Diphenyl-*pp'*-bisdiazonium borofluoride	2296
platinichloride	2253	zincichloride	2270
aurichloride	2260	Diazobenzenesulphonic acid	2282
tetrachloroiodite	2257	Naphthalene-1-diazonium borofluoride	2262
borofluoride	2296	zincichloride	2231
o-Chlorobenzenediazonium ferrichloride	2239	mercurichloride	2234
tetrachloroiodite	2250	cadmichloride	2256
Toluene-*p*-diazonium ferrichloride	2234	Naphthalene-2-diazonium borofluoride	2291
platinichloride	2254	zincichloride	2250
aurichloride	2255	cadmichloride	2250
p-Nitrobenzenediazonium borofluoride	2306		

The figures are centred around 2261 cm.$^{-1}$ (with standard deviation, $\pm$21 cm.$^{-1}$), this is of the order to be expected for a triple linkage and thus provides physical evidence for the modern equivalent of Blomstrand's formulation of diazonium salts (see Sidgwick, Taylor, and Baker, "Organic Chemistry of Nitrogen," Oxford, 1937, p. 413). Moreover, since the spectra near 2260 cm.$^{-1}$ are clear of other group effects, the occurrence of such absorption may reasonably be accepted for the purpose mentioned at the outset.

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Reactions in Alcohol–Phosphorus Tribromide Systems.

By W. Gerrard and H. Herbst.

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Alkyl phosphorodichloridites, $PCl_2{\cdot}OR$, and chloridites, $PCl(OR)_2$, are quickly formed during the addition of an alcohol such as butan-1-ol to phosphorus trichloride (Gerrard, Isaacs, Machell, Smith, and Wyvill, *J.*, 1953, 1920; Gerrard and Shepherd, *J.*, 1953, 2069), and their properties are of significance in the description of alcohol–phosphorus trichloride systems. It was therefore necessary to examine the corresponding dibromidite and bromidite, in order to describe phosphorus tribromide systems. Already a general resemblance between the two systems was apparent (Gerrard, *J.*, 1945, 848; Gerrard and Whitbread, *J.*, 1952, 914); but the more vigorous dealkylating power of hydrogen bromide, compared with hydrogen chloride, made it difficult to follow the sequence of reactions which occur when such an alcohol is added to phosphorus tribromide.

By carefully removing hydrogen bromide before distillation, *n*-butyl phosphorodibromidite was prepared from butan-1-ol (1 mol.) and the tribromide (1 mol.) (reaction 1); but alkyl bromide, the tribromide, and undistillable material were also isolated, for, as is clear from the trichloride system, reactions (2) and (3) probably occurred concurrently, and dealkylation of the esters produced gives alkyl bromide. The dibromidite was stable at 100° (2 hr.), but slowly decomposed at 160°, giving alkyl bromide, undistillable

$$\text{(1)} \quad ROH + PBr_3 \longrightarrow PBr_2{\cdot}OR + HBr$$

$$\text{(2)} \quad ROH + PBr_2{\cdot}OR \longrightarrow PBr(OR)_2 + HBr$$

$$\text{(3)} \quad ROH + PBr(OR)_2 \longrightarrow P(OR)_3 + HBr$$

products, and, unexpectedly, phosphorus tribromide. This decomposition was to some extent facilitated by pyridine hydrobromide. An alkyl bromide and phosphorus tribromide were also slowly formed when the dibromidite reacted with hydrogen bromide at 22°. The slowness of the dealkylation is in accord with the mechanism previously discussed (Gerrard and Whitbread, *loc. cit.*); but the formation of phosphorus trihalide by the two procedures was not observed in the trichloride system, probably owing to experimental factors and the slowness of the reactions.

Di-*n*-butyl phosphorobromidite could not be obtained by using more alcohol [reaction (2)], but was prepared by the addition of a mixture of alcohol and pyridine to the dibromidite. It decomposed on being stored at 15°, and at 100° afforded alkyl bromide in 90% yield in 2 hr. When the ester was dealkylated by hydrogen bromide, alkyl bromide (1 mol.) was formed in 4·5 hr. at 25°.

Experiments with *sec.*-butyl and *iso*butyl esters afforded similar results, except that *iso*butyl bromide was accompanied by *tert.*-butyl bromide when obtained by thermal decomposition of the dibromidite.

Experimental.—Reagents were rigorously purified. Specimens of alkyl bromides were characterised by b. p., n_D, and bromine content. They were always withdrawn from reaction mixture at low pressure, and trapped.

Preparation of the dibromidites. The alcohol (1 mol.) was added dropwise to phosphorus tribromide (1 mol.) at −15°, hydrogen bromide being swept away by a stream of dry carbon dioxide. It is imperative to remove hydrogen bromide before distillation. Alkyl bromide and phosphorus tribromide were isolated, and there was always an undistillable residue. Results are recorded in Table 1.

Preparation of the bromidites. The alcohol (1 mol.) and pyridine (1 mol.) in ether (20 mols.) were added to the dibromidite (1 mol.) in ether (20 mols.) at −15°. Base hydrobromide (100%) was immediately precipitated, and from the filtrate, the *bromidite* (see Table 2) was obtained with some difficulty, owing to its instability. The bromidites decomposed on being stored at 15°, and on being heated at 100° for 2 hr., gave the alkyl bromide (Bu^n, 0·90; Bu^s, 0·83; Bu^t, 0·62 mol.).

Dealkylation of the bromidites. Hydrogen bromide was passed into the bromidite (1 mol.) for the time and at the temperature stated. Alkyl bromide was withdrawn at 15 mm., and the residue was always undistillable. The *n*-butyl ester (7·35 g.) gave, at 25°, butyl bromide (3·9 g., 1 mol., after 4·5 hr.; 4·6 g., 1·2 mol., after 24 hr.) and a residue (4·1 g.). The

TABLE 1.

ROH		Phosphorodibromidites						Residue,
R	g.	Yield (%)	B. p./mm.	n_D^{20}	d_4^{20}	Br (%) *	P (%) *	g.
Bu^n	2·9	57	38°/0·01	1·5441	—	60·7	11·2	0·9
Bu^i	5·95	56	64°/5	1·5391	1·768	60·4	11·5	3·0
Bu^s	6·7	35	38°/0·1	1·5409	1·798	61·1	11·2	4·1

* $C_4H_9OBr_2P$ requires Br, 60·6; P, 11·7%.

*iso*butyl ester (5·5 g.) gave, at 21°, alkyl bromide (2·1 g., 0·71 mol., after 20 hr.) and a residue (4·0 g.). The *sec.*-butyl ester (6·95 g.) gave, at 21°, the alkyl bromide (3·7 g., 1 mol., after 7 hr.; 4·0 g., 1·08 mol., after 24 hr.) and a residue (3·5 g.).

Thermal stability and dealkylation of the dibromidites. The *n*-butyl ester (8·03 g.) was slowly heated to 100° (2 hr.), but the liquid remained colourless, and no alkyl bromide could be withdrawn at low pressure. At 160°, decomposition was obvious; after 2 hr. *n*-butyl bromide (1·25 g., 30%), phosphorus tribromide (3·45 g.), b. p. 23°/0·01 mm. (Found: Br, 86·0. Calc. for PBr_3: Br, 88·5%), butyl dibromidite (2·06 g.), b. p. 38°/0·01 mm. (Found: Br, 60·9%), and a residue (0·23 g.) were obtained. Similarly, the *iso*butyl ester (4·05 g.) gave a mixture

TABLE 2.

PBr_2·OR		Phosphorobromidites			
R	g.	Yield (%)	B. p./mm.	n_D^{20}	Br (%) *
Bu^n	5·71	42	50°/0·05	1·4690	31·1
Bu^i	4·22	45	64°/0·4	1·4535	30·9
Bu^s	4·50	40	32—34°/0·05	1·4598	31·9

* $C_8H_{18}O_2BrP$ requires Br, 31·1%.

(0·71 g., 34%) of *iso*butyl bromide (40%) and *tert.*-butyl bromide (60%), as well as phosphorus tribromide (0·9 g.), b. p. 24°/0·02 mm. (Found: Br, 85·7%), butyl dibromidite (1·08 g.), b. p. 32°/0·2 mm. (Found: Br, 60·9%), and a residue (0·9 g.). The *sec.*-butyl ester (4·61 g.) decomposed about 118°, and after 3 hr. gave *sec.*-butyl bromide (1·08 g., 45%), phosphorus tribromide (1·01 g.), b. p. 23°/0·01 mm. (Found: Br, 87·0%), butyl dibromidite (1·2 g.), b. p. 38°/0·1 mm. (Found: Br, 61·0%), and a residue (0·9 g.).

The dibromidites were heated at 100° for 2·5 hr. in the presence of pyridine hydrobromide (1 mol.), which was unchanged at the end (Found: Br, 49·5. Calc.: Br, 50·0%). The *n*-butyl ester (7·88 g.) gave *n*-butyl bromide (1·46 g., 35·7%), phosphorus tribromide (2·2 g.), b. p. 23°/0·01 mm. (Found: Br, 87·5%), and butyl dibromidite (2·81 g.), b. p. 38°/0·01 mm. (Found: Br, 60·0%). The *iso*butyl ester (4·71 g.) gave a mixture of *iso*butyl (0·28 g.) and *tert.*-butyl (0·42 g.) bromide, phosphorus tribromide (1·01 g.), b. p. 22°/0·01 mm., and butyl dibromidite (2·20 g.) (Found: Br, 60·8%).

Dry hydrogen bromide was passed into the ester at 22°, and effluent gas was passed through a trap at −40°. The rate of production of alkyl bromide was followed by withdrawing volatile matter. The *n*-butyl ester (3·47 g.) gave after 8 hr. *n*-butyl bromide (1·6 g., 89%), and phosphorus tribromide (2·1 g.), b. p. 23°/0·02 mm. (Found: Br, 87·0%). The *iso*butyl ester (4·74 g.) gave, after 23·5 hr., *iso*butyl bromide (1·96 g., 79·5%), phosphorus tribromide (0·9 g.) (Found: Br, 87·4%), butyl dibromidite (0·97 g.) (Found: Br, 60·0%), and a residue (1·55 g.). The *sec.*-butyl ester (4·7 g.), after 24 hr., gave *sec.*-butyl bromide (2·2 g., 89·5%), phosphorus tribromide (2·5 g.), b. p. 23°/0·01 mm. (Found: Br, 86·0%), and a residue (1·01 g.).

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The Electrical Conductivities of Phosphorus and Antimony Trifluorides.

By A. A. Woolf.

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The conductivities of phosphorus and antimony trifluorides have been measured during an investigation of Group v double fluorides. To determine whether Ruff and Plato's antimony trifluoride–antimony pentafluoride compounds (*Ber.*, 1904, **37**, 673) were ionic, the conductivities of antimony trifluoride in the pentafluoride and of the pentafluoride in the trifluoride were required. Antimony trifluoride appeared to be insoluble in the pentafluoride and failed to increase its conductivity. This is in agreement with other observations which show that the pentafluoride is not an ionizing solvent. The conductivity of the trifluoride was then measured and is of the same order as that of fused zinc chloride (*ca.* 10^{-2} mho). The values obtained were approximate, because of experimental difficulties, so that measurements with quinquevalent antimony solutions were not attempted. The high conductvity of antimony trifluoride is of interest because it demonstrates again that the conductivity of a melt is not necessarily related to that of the solid structure. Both aluminium trichloride, which has a two-dimensional ionic lattice (Ketelaar, MacGillavry, and Renes, *Rec. Trav. chim.*, 1947, **66**, 501), and phosphorus pentachloride with a three-dimensional ionic lattice (Clark, Powell, and Wells, *J.*, 1942, 642) possess negligible conductivities in their melts (Biltz, Klemm, and Voigt, *Z. anorg. Chem.*, 1923, **126**, 39; 1924, **133**, 277), whereas the molecular lattices of antimony trifluoride (Bystrom and Westgren, Gmelin's "Handbuch," 8th edn., 1949, Vol. XVIII, *B*, p. 395) and di-iodine hexachloride (Boswigk and Wiebenga, *Acta Cryst.*, 1954, **7**, 417) give highly conducting melts (Greenwood and Emeléus, *J.*, 1950, 987).

Phosphorus trifluoride had the expected low conductivity in the liquid state (10^{-9} mho). The liquid had a negative temperature coefficient of conductivity and obeyed Ohm's law. Thus the conductivities of the trifluorides so far measured increase from phosphorus to arsenic (10^{-5} mho) to antimony and it would be surprsing if the ionic bismuth trifluoride did not continue in this sequence. The relation between the conductivities of fluorides and the rates of complex formation with alkali fluorides—that only liquid fluorides with conductivities of $\ll 10^{-5}$ mho react at an appreciable rate—holds for the other Group v fluorides subsequently examined (Woolf and Greenwood, *J.*, 1950, 2200). When an excess of antimony trifluoride was melted with potassium fluoride for a few minutes and then frozen and the antimony trifluoride was sublimed off *in vacuo*, a solid residue $KF,0{\cdot}36SbF_3$ was obtained, probably a potassium fluoride–potassium tetrafluorometa-antimonite mixture. Potassium fluoride failed to combine wth phosphorus trifluoride at room temperatures during three months. Lange and Stein (unpublished work reported in Simon's "Fluorine Chemistry," Academic Press Inc., New York, 1950, Vol. I, p. 139) found that hot potassium fluoride absorbed phosphorus trifluoride, but we found no combination when phosphorus trifluoride was passed over potassium fluoride *in vacuo* at temperatures up to 240°. At atmospheric pressure and temperatures above 200° an apparent combination occurred but the red product indicated that some phosphorus trifluoride had disproportionated to phosphorus. The concomitant phosphorus pentafluoride can combine with alkali fluorides at these temperatures.

Ruff and Schiller (*Z. anorg. Chem.*, 1911, **72**, 329) have already shown that liquid niobium and tantalum pentafluorides combine with potassium fluoride at an appreciable rate in conformity with the conductivities of these liquids (Fairbrother, Frith, and Woolf, *J.*, 1954, 1031). It is unlikely that the product was the heptafluoro-salt as they suggest, because an excess of pentafluoride was used. The product with even 2 : 1 ratios of alkali fluoride to niobium pentafluoride in anhydrous hydrogen fluoride or bromine trifluoride is exclusively the hexafluoroniobate (Laubengayer and Polzer, *J. Amer. Chem. Soc.*, 1941, **63**, 3264; Gutmann and Emeléus, *J.*, 1950, 1046).

The only Group v fluoride for which it is difficult to predict the conductivity is vanadium pentafluoride. This value may be higher than the position of vanadium in the Group would indicate, since the pentafluoride combines readily with potassium fluoride.

Experimental.—Conductivity of antimony trifluoride. The trifluoride was recrystallised from methanol, to remove oxide and oxyfluoride (Bak and Hillebert, *Acta Chem. Scand.*, 1953, **7**, 236). The purified trifluoride, contained in an aluminium cup surrounded by an external furnace, was sublimed *in vacuo* on to a water-cooled copper condenser. The choice of electrode insulators for the metal cells proved difficult. Fluorides are unsuitable because of possible combination with antimony trifluoride, and oxides may be converted into fluorides. A cemented asbestos was used in these experiments. In one type of conductivity cell constructed of copper, a pair of brass cylinder electrodes was used. These were not absolutely inert. In another type of cell a pointed nickel electrode, whose position could be adjusted from outside the furnace by means of a micrometer head, was placed centrally in a platinum bottle by means of the asbestos insulator. The bottle served as the other electrode. Contact of the rod electrode with the electrolyte could be detected by completing a circuit, after which the electrode was lowered to a fixed position by the micrometer head. With both cells attack on the insulator was severe enough to invalidate any but the initial few readings. A value of 0·065 mho at 300° obtained in the copper cell was close to that in the platinum cell (0·067 mho at 316°). The solid trifluoride appeared to conduct well in the solid state Even 100° below the m. p. the conductivity was about 10^{-6} mho.

Conductivity of phosphorus trifluoride. The trifluoride was prepared by halogen exchange between phosphorus trichloride and antimony trifluoride (Booth and Bozarth, *J. Amer. Chem. Soc.*, 1939, **61**, 2927) and purified by vacuum-fractionation. The purity of the trifluoride was shown by the absence of any chlorine-containing products. A Pyrex-glass conductivity cell (constant 0·118), the platinum electrodes of which were joined to the Pyrex glass by graded seals, was connected to a gas bulb and final purification train. The conductivity was measured with direct current after Ohm's law had been established in the liquid. The slope of the voltage–current curve gave a value of $0{\cdot}42 \times 10^{-9}$ mho at 113°.

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